# SERUM TESTOSTERONE LEVELS IN MALE COPD PATIENTS

*Dissertation submitted to*

**THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY**

*In partial fulfillment of the regulations*

*For the award of the degree of*

**M.D. GENERAL MEDICINE (BRANCH - I)**

**INSTITUTE OF INTERNAL MEDICINE**

**MADRAS MEDICAL COLLEGE**

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**THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY**

**CHENNAI**

**APRIL 2015**

# CERTIFICATE

This is to certify that the dissertation titled **"SERUM TESTOSTERONE LEVELS IN MALE COPD PATIENTS"** is the bonafide original work of **Dr. D.HENITH RAJ** in partial fulfillment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamilnadu DR. M.G.R Medical University to be held in APRIL 2015. The Period of study was from July 2014 to September 2014.

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# DECLARATION

I, **Dr. D.HENITH RAJ** solemnly declare that dissertation titled **"SERUM TESTOSTERONE LEVELS IN MALE COPD PATIENTS"** is a bonafide work done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 during July 2014 to September 2014 under the guidance and supervision of my unit chief **Prof. K.S.CHENTHIL, M.D** Professor of Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree (Branch – I) in General Medicine – APRIL 2015.**

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# ACKNOWLEDGEMENT

No endeavour can start, continue and complete without the blessing of almighty god and I thank him for always being by my side.

I would like to thank our dean, **Dr. R.VIMALA M.D**, Madras Medical College, Chennai for providing the facilities for this study.

Words fall short to describe my deep sense of gratitude and respect that express my utmost thanks to my guide, **Dr. K.S. CHENTHIL M.D,** Professor of Medicine, Madras Medical College, Madras, a teacher with excellent clinical skills and knowledge for his unfailing inspiration, affectionate guidance and advice throughout the course of the present study. His valuable suggestions, sympathetic, helping nature and encouragement enabled me to attain this achievement.

My special thanks to my co- guide **Dr. D. RANGANATHAN M.D**, professor of Thoracic Medicine for his constant encouragement and guidance throughout the course of this study.

It is with immense honour and gratitude that I specially thank **Dr.S.TITO M.D**, Prof of Medicine, Madras Medical College for his constant support and encouragement throughout the course.

I would like to thank our Assistant Professors. **Dr. P. Anusuya M.D** and **Dr. D. K. Sivakumar. M.D** for their kind encouragement.

I would like to express my sincere thanks to my scholarly batch mates, colleagues, interns and friends who were always ready to help me even at odd hours.

I sincerely thank all the patients who helped me in my study without whom this study would not have been possible.

My family is the reason I am here today - my parents and sister whose cherished blessings and countless sacrifices are behind whatever success I have achieved in my life. I take this opportunity to thank them all and I am forever indebted to them.

**D. Henith Raj**

# CONTENTS

# ABSTRACT AND KEYWORDS

Under the clinical impression that COPD is associated with low testosterone levels, we investigated this association. We selected 100 male COPD patients and categorized them according to GOLD criteria. Serum testosterone levels of these patients were measured. We sought a significant association between severe COPD and testosterone levels. 34 of the 100 patients had low testosterone levels.The conclusions of our study were i) patients in GOLD stage IV had higher probability of having low testosterone levels ii) Patients had higher risk of low testosterone levels with decreased oxygen saturation iii) Patients showed a tendency of decreasing BMI with increasing severity iv) Patients on long term glucocorticoid treatment had higher chances of having low testosterone levels.

Thus low testosterone levels are frequent in COPD with increasing severity. Testosterone replacement therapy has already been tried in this setting. Further studies are required before routine recommendations can be made.

# INTRODUCTION

Testosterone is the most important androgen in males. Biosynthesis of testosterone occurs mainly in the adult Leydig cells. The daily testicular output of testosterone is between 3-10 mg.

Being the principal circulating androgen from the adult testes, testosterone has a negative-feedback action on pituitary secretion of gonadotropins. The biologically active fraction of testosterone is the free circulating form which constitutes about 2% of the total circulating form, the remainder being bound to SHBG (60%) and albumin (38%).

Testosterone levels are decreased in a variety of disease states. The mechanisms which contribute to this state vary. This state of hypogonadism in males causes further impairment of quality of life in addition to that caused by the underlying disease state.

Low testosterone levels in chronic diseases have an independent effect on mortality which has been shown by studies. Trials on Testosterone replacement therapy in these diseases have been done with encouraging results.

Chronic Obstructive Pulmonary disease (COPD) is rampant in our country. The mortality rate in severe COPD remains high. Low testosterone level is one of the important contributors to this mortality. Hence an attempt

has been made to study the serum Testosterone levels in male COPD patients at the Institute of Internal Medicine, Madras Medical College.

# AIMS AND OBJECTIVES

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1) To study the prevalence of low Testosterone levels in male COPD patients.
2) To correlate the prevalence of low testosterone levels in COPD with disease duration and severity.

# REVIEW OF LITERATURE

# REVIEW OF LITERATURE

## CHRONIC OBSTRUCTIVE PULMONARY DISEASE

### Definition:

COPD encompasses a group of diseases rather than a single disease. (Chronic Bronchitis, Small Airways disease &Emphysema)

The characteristic of COPD, airflow limitation is a result of small airway disease and destruction of lung parenchyma.

Chronic Bronchitis is clinically defined as *"the presence of chronic productive cough on most days for three months, in each of two consecutive years after ruling out other causes of chronic cough"*. The three forms of chronic bronchitis are

1) Simple bronchitis
2) Chronic or Recurrent mucopurulent bronchitis
3) Chronic Obstructive bronchitis

Emphysema is defined as *"abnormal, permanent enlargement of the distal air spaces (distal to terminal bronchioles ) accompanied by destruction of their walls without obvious fibrosis"*.

Small airways disease/ Obstructive bronchiolitis is due to inflammation, squamous cell metaplasia and/ or fibrosis in airways less than 2 mm diameter. It is one of the earliest changes that occur in smokers[1].Its contribution to the airflow obstruction increases as the disease progresses[2].

The relative contribution made by airway abnormalities or distal airspace enlargement to airflow limitation in a COPD individual is difficult to determine. Thus the term COPD was introduced in the early 1960s to describe patients with largely irreversible airflow obstruction, due to a combination of airway disease and emphysema.

**EPIDEMIOLOGY:**

COPD is an important disease of much global importance with regards to many factors such as the disease prevalence, burden of morbidity & mortality. The disease prevalence could increase in the near future.

**GLOBAL SCENARIO:**

The worldwide prevalence of COPD in adults > 40 years of age is about 9-10%[3,16]. COPD is the third leading cause death & the fifth leading cause of DALYs worldwide[5].

The COPD prevalence varies among different countries[3]. These variations in prevalence could be attributed to different methods of diagnosis & classification[14]. The COPD prevalence rates are much higher when spirometry is used for diagnosis when compared to clinical symptoms alone[15].

The BOLD (Burden of Obstructive Lung Disease ) study involved 9425 individuals from 12 different sites. Post bronchodilator spirometry testing was used to assess the prevalence of COPD in this study. The overall prevalence of GOLD stage ≥ II was 10.1% ( men-11.8% , women- 8.5% ). This study brought out regional differences in COPD prevalence worldwide. Among men the figures varied from as high as 22% in Cape Town, South Africa to 9% in Reykjavik, Iceland. The prevalence among women was no exception with 4% in Hannover, Germany to 17% in Cape Town, South Africa[17].

The PLATINO study was conducted in South American countries to assess the COPD burden. This study also used post bronchodilator spirometry for finding out the prevalence of COPD. The study showed that the COPD prevalence in the 5 Latin American countries studied was 14.3% ( GOLD stage ≥ II – 5.6% )[18]. Similarly a Chinese study showed that the prevalence of COPD varied from 5-13% in different provinces of China[19].

**INDIAN SCENARIO:**

An Indian study done recently to study the prevalence of Asthma, Chronic bronchitis & respiratory symptoms concluded that the prevalence of chronic bronchitis in adults > 35 years was around 3.49%[3].

The contribution of India to the total global mortality of COPD is quite significant with the recent figures showing about 102.3/ 1 lac population[4]. COPD has already overtaken Malaria & Tuberculosis as a leading cause of morbidity & mortality in India[4]. The burden of COPD is not uniformly distributed across India. The recently conducted INSEARCH study enrolled 85105 men & 84470 women from 11 rural & 12 urban areas. It showed that the prevalence of COPD in Mumbai (Western India ) was 1.1% whereas in Trivandrum ( Southern India ) it was an alarming 10%[3]. The study concluded that the national burden of COPD to be 14.84 million[3].

The distribution of COPD varies among various subpopulations & within subpopulations. Many factors influence the disease distribution. For example, COPD is a disease of older age groups & is rare in young individuals unless he/she has a strong genetic predisposition like alpha-1 antitrypsin deficiency[8].There is a strong male preponderance in COPD. This could be due to increased rates of tobacco smoking among men particularly in India[6,7,8]. The male:female ratio & the smoker:non-smoker ratio in India are not as high as it is in the western countries[6,9]. The above mentioned

differences could largely be due to the widespread usage of biomass fuel for cooking & indoor air pollution[10-13]. Passive smoking (tobacco smoke exposure from household males) is also a contributory factor to the above difference[6]. Although the INSEARCH study showed variations according to geographic locations in COPD prevalence, a study conducted by Jindal et al showed that the sex differences in COPD prevalence were similar across the country[9].

**AETIOLOGY:**

COPD results from the interplay of genetic & environmental factors**.**

**ENVIRONMENTAL FACTORS:**

**1) Tobacco smoke:**

Smoking is the most important risk factor for developing COPD[3,4]. Previously it was thought that only 10-20% of smokers develop clinically significant COPD. Now it has been proved that it is a gross underestimate. The risk of developing COPD is directly related to the total tobacco exposure. Despite smoking being the most important risk factor for developing COPD, about 10% of COPD patients are non-smokers. Thus it is obvious that although smoking is a crucial factor, additional factors play a major role in the development of COPD.

One of the most important evidences that link smoking with COPD comes from the United Kingdom. A study was conducted between 1953 & 1967 in the UK among doctors & the general population. All the participants were asked to record their smoking habits. The mortality rate due to chronic bronchitis in the doctor's wing fell by a staggering 24% whereas in the general wing it fell by a meagre 4%. The above difference in mortality rates was attributed to decreased smoking among doctors as compared to the general population.

Effects of smoking on the respiratory system are

a) Increase in prevalence of respiratory symptoms
b) Abnormalities in lung function
c) Increased rate of $FEV_1$ decline per annum
d) Greater mortality rate compared to non-smokers

**2) Passive Smoking:**

Passive smoking can lead to the development of respiratory symptoms & airflow limitation (Environmental tobacco smoke)[20,21]. There is evidence that increased amount of environmental tobacco smoke exposure in childhood could lead to a decrease in the peak $FEV_1$ level that can be achieved in adulthood. It is a well known fact that antenatal smoking is

coupled with low birth weight & smoking by either parent increases the incidence of respiratory illnesses in the first three years of life. These associations suggest that environmental tobacco smoke could have an effect on the immune system.

**3) Outdoor air pollution:**

This is a major problem in industrialized regions & metropolitan cities. Among the outdoor air pollutants, particulate pollutants (eg. Sulphur di-oxide)play a major role in the exacerbation of airways disease & COPD[23]. The association between decline in lung function & outdoor air pollution has been shown by various longitudinal studies[22]. Photochemical air pollutants (eg. Nitrogen di-oxide, Ozone) are more of an important factor in Asthma rather than COPD**.**

**4) Indoor air pollution:**

This is a more common setting in the under developed countries. Overcrowding, usage of biomass fuel for cooking are important causes of indoor air pollution[10-13,24]. These factors are more important in the development of COPD in women particularly in cultures where female smoking is not common.

**5) Chronic bronchopulmonary infection:**

Bronchopulmonary infections play a crucial role in the natural course of COPD. Prophylactic antibiotics do not appear to protect against recurrent COPD exacerbations due to infections. This has been proved by various studies some of which have been conducted as early as the 1960s & 70s. Earlier it was thought that respiratory infections lead to acute decline in lung function in COPD patients which was totally reversible on clearance of the infection. More recent data have challenged this view and they have suggested that recurrent bronchopulmonary infections lead to progressive worsening of $FEV_1$[25].

Symptoms of cough & sputum production in the age group of 20-35 years are more common among those who have had childhood history of severe lower respiratory illness. This association between childhood respiratory illness & adulthood decline in lung function is probably due multiple reasons such as passive smoking, low socioeconomic status, overcrowding, exposure to high amounts of pollution.

**6) Occupation:**

Causal relationship between occupational dust exposure and COPD is a generally accepted fact. In this setting, smoking is often a confounding factor

due to the high prevalence of smoking habits among people engaged in these occupations. Various longitudinal studies have shown the link between progressive worsening of $FEV_1$ and occupational dust exposure[26-28].Among patients with respiratory symptoms or pulmonary function abnormalities consistent with COPD, 10-20% of cases are attributed to long term occupational dust exposure. The government of United Kingdom brought COPD under the list of diseases considered for compensation in miners following accumulating evidence of association between coal dust exposure and COPD. Others occupations that are associated with increased COPD risk include welding, Shipyard work, Cadmium exposure etc. Increased incidence of emphysema among workers exposed to cadmium has been shown by studies[29].

Not all occupational dusts are equally effective in promoting the development of COPD. For example, a study done by Oxman et al showed that workers involved in gold mining had a triple fold risk of developing COPD when compared to those working in coal fields[26]. This difference could be due to the increased silica content in gold mines.

**7) Diet:**

There is growing evidence that some of the dietary habits could be linked to the development of COPD. A study done in Britain has brought out the correlation between dietary consumption of fresh fruits and ventilator function, both in smokers and non-smokers. There is evidence that low plasma ascorbic acid levels are associated with increased risk of developing COPD. This could be due to increased incidence of pneumonias among Vitamin C deficient individuals[30].

**8) Socioeconomic factors:**

Low socioeconomic status is associated with the development of COPD[7,31]. The cause is multifactorial such as overcrowding, indoor air pollution etc**.**

**HOST FACTORS:**

**1) Genetic factors:**

Genetic susceptibility to COPD has been shown by the increased familial risk of acquiring significant airflow limitation in smoking siblings of

patients with severe COPD. Genetic studies have revealed various genes that are linked to the development of COPD. Some of the genes are

a) Microsomal epoxide hydrolase-1
b) Tumour necrosis factor ( TNF )
c) Transforming growth factor β ( TGFβ )

Genetic linkage analysis has revealed various regions in the genome that could contain COPD susceptibility genes eg. Chromosome 2q. However the strongest genetic link with COPD is the $alpha_1$ antitrypsin deficiency.

**2) Gender:**

Traditionally COPD has been more common among men when compared to women. However in recent times this gender gap has narrowed. This could possibly be due to the increased female smoking. It has been proposed that females are more prone to the ill effects of tobacco smoke. But gender as a risk factor for COPD is a question that is far from resolved.

**3) Atopy& Airway hyperresponsiveness:**

In the 1960s, the “Dutch hypothesis” was proposed. It stated that *“smokers with chronic, largely irreversible airways obstruction and subjects*

*with asthma shared a common constitutional predisposition to allergy, airway hyperresponsiveness, and eosinophilia"*.It has been shown by various studies that smokers have higher serum IgE levels & eosinophil counts when compared to non smokers[32]. Asthmatic patients have the same pattern[33] but the levels are much higher when compared to COPD patients. Atopic status shows no variability among smokers and non-smokers& whether airway hyperresponsiveness is a cause or consequence of COPD is debatable.

**4) Factors acting in gestation:**

Mortality from chronic pulmonary diseases varies inversely with birth weight & weight at one year of age. Thus impaired growth in utero, particularly impaired lung growth drastically increases the chances of an individual developing COPD.

**OTHER CONSIDERATIONS:**

**Chronic mucus hypersecretion:**

Smokers have a higher incidence of respiratory symptoms and mucus production. Cessation of smoking leads to the cessation of mucus hypersecretion in about 90% of cases. The British hypothesis stated that *"Chronic airflow limitation resulted from the development of chronic mucus*

*hypersecretion as a result of recurrent bronchial infection"*.This hypothesis was tested in the studies conducted by Fletcher &Peto among London's working men. This study showed that there was a progressive decline in $FEV_1$ among smokers but it failed to demonstrate a correlation between declining $FEV_1$ and the degree of mucus hypersecretion. However a study conducted in Copenhagen between 1976 & 1994 showed that mucus hypersecretion was associated with increased rates of hospital admission and a progressive decline in $FEV_1$.

**Morbidity/ Use of health resources:**

COPD has a huge impact on the usage of health care resources including outpatient visits, hospitalization & ICU care. The economic burden imparted by COPD is more than twice that of Asthma. The frequent exacerbations in COPD patients further affects the quality of life.

In the European Union, respiratory diseases account for 6% of the total direct health expenditure and COPD accounts for 56% of it. The cost of care of COPD and the severity of the condition are directly related.

Years of living with disability (YLD) can be calculated to estimate the morbidity burden of the disease. The global figure is around 1.68 YLD/1000

populations, which represents 1.8% of all years of living with disability, with a major effect in men.

**Mortality:**

In USA and Europe, COPD is the fourth leading cause of death. COPD is a growing epidemic worldwide. By the end of 2020, COPD could well be the third leading cause of death worldwide.

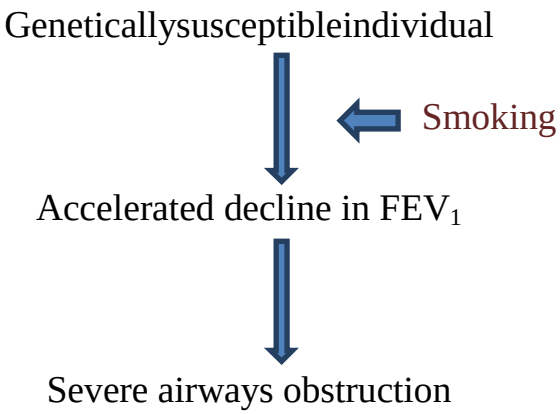
There are wide international variations in COPD mortality. These variations cannot be entirely attributed to differences in diagnostic patterns, smoking habits etc. COPD is a contributing factor in various other causes of death. Thus the true mortality due to COPD could well be far higher than the current estimates[34].

**Natural history & Prognosis:**

COPD is generally progressive, particularly if the exposure to the noxious agent continues. However, the natural history of COPD is highly variable among individuals. Cessation of noxious agent exposure (eg. Smoking) could possibly halt disease progression.

The average decline of $FEV_1$ in non-smokers is 20-30 ml/year. In smokers there is an accelerated rate of $FEV_1$ decline at 50 ml/year. In addition lower respiratory tract illnesses promote $FEV_1$ decline in active

smokers[35]. The study done by Fletcher and colleagues among working men in London gave valuable insights into the course of COPD. The study was a follow up study of 8 years duration. The study showed that it was possible to pick up susceptible cigarette smokers early in mid life by a reduction in $FEV_1$. A tracking effect was suggested by the study (ie) persistence of individuals in the same percentiles over subsequent years irrespective of whether they were in the highest or lowest $FEV_1$ percentiles initially.




The rate of decline in $FEV_1$ varies during the progression of the disease. There is a tendency for slower declines in $FEV_1$ in advanced disease when compared to mild disease.

The strongest predictors of survival in COPD patients are

a) Age

b) Baseline $FEV_1$

The five year mortality rate in COPD patients with $FEV_1 \leq 30\%$ is more than 50% and the relationship between post bronchodilator $FEV_1$ and survival is even stronger. Other predictors of survival that have been suggested are the 6 minute walk distance[36] and exercise capacity[37]. Other unfavourable prognostic factors are

a) Severe hypoxaemia
b) Low CO transfer
c) Raised pulmonary artery pressure
d) Weight loss

**Pathology:**

The pathological changes that occur in the respiratory system in COPD patients are complex. Basically, changes occur in three compartments. They are

a) Large airways
b) Small airways
c) Alveoli

The relative contribution of the three compartments in the airflow obstruction in a given patient is a subject of considerable study[40,44]. The correlation between the pathologic changes and both clinical & functional patterns of disease is generally poor. There is still no unity of thought

regarding the cause of fixed airway obstruction in COPD (ie) due to either inflammation & scarring in small airways or to the loss of support for the airways due to loss of alveolar walls. Although the pathological changes in COPD occur in the above mentioned compartments, in a given patient abnormalities may coexist in all the three compartments rather than in one compartment.

The characteristic features of COPD are

a) Poorly reversible airflow obstruction
b) Abnormal inflammatory response in the lungs[43]

The abnormal inflammatory response in lungs is due to innate and adaptive immune responses to noxious agents. Pulmonary inflammatory response occurs in all cigarette smokers but an abnormal or increased immune response occurs in those who develop COPD[43]. The results of an amplified immune response are tissue destruction, mucus hypersecretion, small airway inflammation and fibrosis. These pathological changes result in air trapping & progressive airflow limitation due to increased impedance to airflow in small airways & increased pulmonary compliance.

**Chronic Bronchitis:**

The cause of mucus hypersecretion[41] that occurs in chronic bronchitis is due to

a) Increase in the volume of submucosal glands.
b) Increase in the number of goblet cells
c) Change in the goblet cell distribution in the surface epithelium

In normal circumstances, submucosal glands are confined to the larger bronchi, decreasing in size and number in the smaller bronchi and not present in the bronchioles. In the setting of chronic bronchitis, the submucosal glands hypertrophy with inflammatory cell infiltration.

In a similar way, in healthy individuals who have never smoked, goblet cells are more commonly seen in the proximal airways with declining trends towards the distal airways and total absence in the respiratory bronchioles. The mucociliary escalator mechanisms are poorly developed in the distal airways. In smokers,goblet cells increase in number and extend peripherally. Thus great quantities of mucus are produced in the distal airways where mucociliary mechanisms are poorly developed. In addition, smokers exhibit poor mucociliary function.

The role of inflammation in chronic bronchitis has been studied using bronchial biopsies. There is a clear evidence of bronchial wall inflammation in this condition. Activated T lymphocytes are found in the bronchial walls of these patients. This is a feature that is shared also by asthma. But in contrast to asthma, the T cells seen in chronic bronchitis are of CD8 subtype rather than CD4 and macrophages are also seen in addition to the CD8 cells. Neutrophils are predominantly seen infiltrating the glands which increases in number as the disease progresses[45,46].

Bronchial biopsies in a few number of studies have shown that there are increased number of eosinophils in the bronchial walls[45]. These numbers are small when compared with acute exacerbations of asthma. In addition, eosinophils seen in asthma usually degranulate whereas in chronic bronchitis they do not.

In patients with chronic bronchitis, increased intraluminal airspace inflammation has been shown by bronchoalveolar lavage and sputum studies. Neutrophils and macrophages[42,47] are the predominant inflammatory cells seen in this type of inflammation. Air space inflammation might not be totally reversible even after smoking cessation.

**Emphysema:**

Emphysema is airway enlargement distal to terminal bronchioles. It is due to the destruction of walls without obvious fibrosis.

According to the enlarged airspace distribution, emphysema has been classified into two major types.

a) Centriacinar ( Centrilobular ) emphysema ( enlarged airspaces are clustered around terminal bronchioles initially)
b) Panacinar ( Panlobular ) emphysema ( airspace enlargement distributed throughout the acinar unit )

Centriacinar emphysema is the common type in COPD. This type is commonly seen in the upper zones of upper and lower lobes. The panacinar variant is more prominent in the lung bases but it can be found anywhere in the lungs. $Alpha_1$ antitrypsin deficiency is associated with the panacinar type. With regards to smoking, it has a clear association with centriacinar emphysema than with panacinar emphysema[48].

Periacinar( Paraseptal/distal acinar ) is an airspace enlargement along the edge of the acinar unitwhere it lies adjacent to a fixed structure like a blood vessel or pleura. This type is less common than the other two types. It carries little clinical significance. In rare circumstances if there is extensive

periacinar emphysema in the subpleural region it can lead on to pneumothorax.

Emphysematous lesions are small ( < 1 mm diameter ) during the early stages of the disease. In due course these lesions may progress to large lesions called bullae[48]. A bulla is a locally over distended area of emphysema. It is usually more than 1 cm size. Bullous disease is not confined to COPD.

The tubular integrity of normal bronchioles and small bronchi is maintained via attachments to the walls of alveoli. In emphysema this arrangement is disrupted which leads to distortion and irregularity of airways.

Similar to the inflammatory cell infiltration seen in the airways, changes are seen in the alveolar walls. Even though absence of fibrosis is a prerequisite for the diagnosis of emphysema, some amount of fibrosis is seen in the terminal bronchioles due to respiratory bronchiolitis that occurs in COPD patients.

**EXTENT OF AIRWAY INFLAMMATORY RESPONSE[38,39]:**

| **COPD STAGE** | **AIRWAYS WITH MEASURABLE NEUTROPHILS(%)** |
|---|---|
| GOLD 0 | 67 |
| GOLD I | 55 |
| GOLD II & III | 84 |
| GOLD IV | **100** |

| COPD STAGE | AIRWAYS WITH MEASURABLE MACROPHAGES ( % ) |
|---|---|
| GOLD 0 | 54 |
| GOLD I | 66 |
| GOLD II & III | 73 |
| GOLD IV | 92 |

| COPD STAGE | AIRWAYS WITH MEASURABLE EOSINOPHILS ( % ) |
|---|---|
| GOLD 0 | 25 |
| GOLD I | 33 |
| GOLD II & III | 29 |
| GOLD IV | 32 |

| COPD STAGE | AIRWAYS WITH MEASURABLE CD4 CELLS ( % ) |
|---|---|
| GOLD 0 | 63 |
| GOLD I | 87 |
| GOLD II & III | 77 |
| GOLD III & IV | 94 |

| COPD STAGE | AIRWAYS WITH MEASURABLE CD8 CELLS ( % ) |
|---|---|
| GOLD 0 | 85 |
| GOLD I | 80 |
| GOLD II & III | 88 |
| GOLD IV | 98 |

| COPD STAGE | AIRWAYS WITH MEASURABLE B CELLS ( % ) |
|---|---|
| GOLD 0 | 7 |
| GOLD I | 8 |
| GOLD II & III | 45 |
| GOLD IV | 37 |

**Bronchiolitis / Small airways disease[44]:**

This concept was introduced by Hogg, Macklem and Thurlbeck. They showed via experiments that the major site of airway resistance in COPD is the small airways. Small airway inflammation is an early change seen in asymptomatic cigarette smokers[50]. These changes are associated with no symptoms initially and considerable amount of change can occur in the airways without causing spirometry changes. The pathological changes found in small airways[49] are

a) Inflammatory cell infiltration in airway wall
b) Mucus and cells in the lumen
c) Goblet cell hyperplasia
d) Airway wall fibrosis[50]
e) Squamous cell metaplasia
f) Mucosal ulceration

g) Increased amount of muscle

h) Pigmentation

Bronchiolitis is a early feature of COPD. Studies conducted in resected lung specimens show that there is a change in the inflammatory response with disease progression. These changes are caused by immune responses to noxious agent exposure for long periods. It has been found that later in the course of the disease there are increased numbers of B cells and lymphoid follicles around the bronchioles. This could represent an autoimmune response to chronic lower respiratory tract infection.

**Pulmonary Vasculature:**

Pulmonary vascular changes are an early feature of COPD. These changes progress through the course of the disease. The end result is pulmonary hypertension and right ventricle dysfunction[51].

INITIAL CHANGES: vessel wall thickening, endothelial dysfunction[52]

PROGRESSION: increased vascular smooth muscle, inflammatory cell infiltration of vessel [52]wall (CD8 cells & macrophages)

LATER STAGES: collagen deposition, emphysematouschanges in alveolarcapillary bed[52]

PULMONARY HYPERTENSION

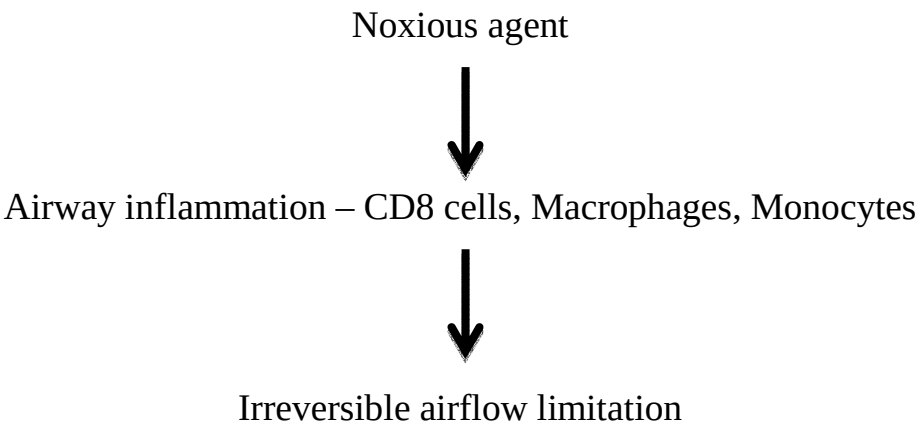
**Pathogenesis:**

Inflammation is invariable in the lungs of smokers. It is a protective response against inhaled toxins. Individuals in whom the inflammatory response is amplified develop COPD. This abnormal inflammation in COPD results in tissue destruction, impaired defence & repair mechanisms[43]. The factors that are key to the pathogenesis of COPD are

a) Amplified inflammation

b) Protease – Antiprotease imbalance

c) Oxidative stress




**Inflammatory cells and mediators:**

The inflammatory cells that are recruited to the lungs secrete a number of cytokines that amplify the inflammatory response. Some of the important mediators are[53-56]

a) Leukotriene $B_4$

b) Chemokines - IL-8

c) Proinflammatory cytokines – TNFα, IL-1β, IL-6

d) Growth factors – TGFβ

**Protease – Antiprotease imbalance:**

$\alpha_1$- antitrypsin deficiency associated early onset emphysema and Papain induced emphysema in rats when instilled into lungs were instrumental in understanding the pathogenesis of COPD. The above two observations laid the foundation for the formation of protease – antiproteasehypothesis[57] which states that *"under normal circumstances the release of proteolytic enzymes from inflammatory cells that migrate to the lungs to fight infection does not cause lung damage because of inactivation of these proteolytic enzymes by an excess of inhibitors"*.If there is an excessive load of enzymes or an absolute or functional deficiency of inhibitors an imbalance develops. This imbalance causes uncontrolled enzyme activity leading to pulmonary alveolar wall connective tissue destruction resulting in emphysema. Some of the important protease – antiprotease combinations are Neutrophil elastase –$\alpha_1$- antitrypsin , serine proteinases –$\alpha_1$- antitrypsin , Cathepsin G – Secretory leukoprotease inhibitor , Cysteine proteinases – Cystatins , Proteinase 3 – Elafin and Matrix metalloproteinases 8,9,12 – TIMP 1-4.

**$\alpha_1$-antitrypsin / $\alpha_1$- protease inhibitor:**

Alpha$_1$-antitrypsin is a polymorphic glycoprotein. It is the most important factor contributing to serum's antiprotease activity[58]. It is produced in the liver. It is an acute phase reactant.The active site of this protein has a methionine-serine sequence upon which its activity depends heavily.

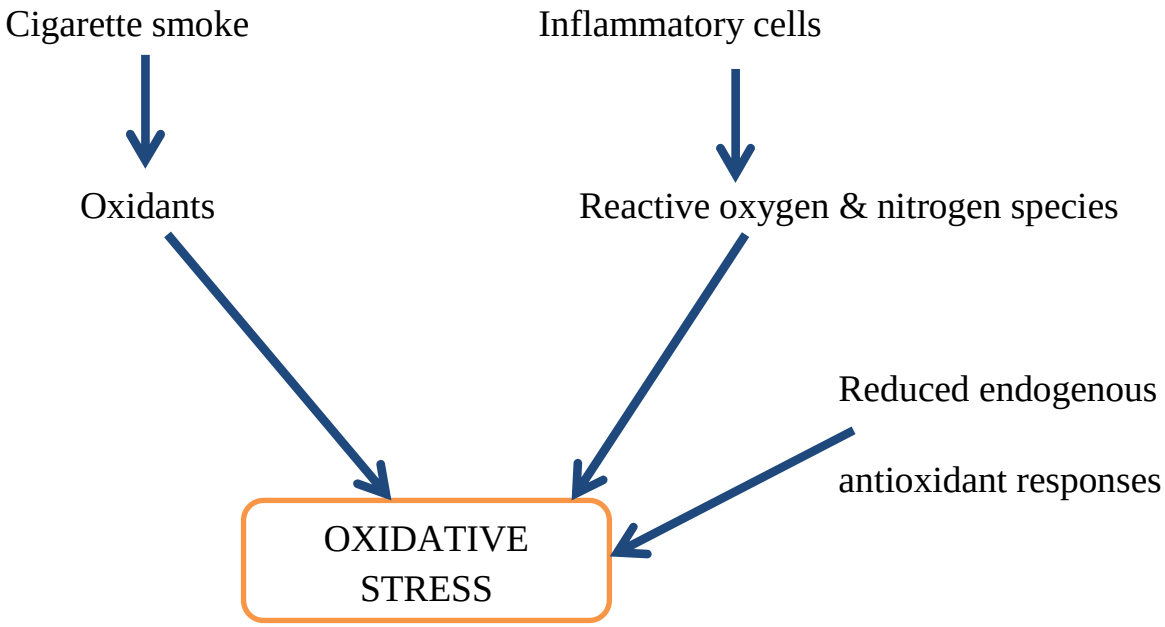
The relationship between $\alpha_1$- antitrypsin deficiency and early onset emphysema was first described by Laurell and Eriksson in 1963. The deficiency is transmitted in an autosomal recessive fashion and over 75 biochemical variants have been identified.

| **PHENOTYPE** | **FREQUENCY** | **EMPHYSEMA RISK** |
|---|---|---|
| MM | 86 % | nil |
| MZ | 3 % | Nil |
| MS | 9 % | Nil |
| ZZ | 0.03 % | Present |
| SZ | 0.2 % | Present |
| SS | 0.25 % | Nil |

Inability to raise $\alpha_1$- antitrypsin levels during acute phase responses leads to undeterred proteolytic damage of pulmonary tissue. Cigarette smoking acts as a cofactor in this setting by creating an oxidative stress which inactivates the remaining functional enzyme.

The prevalence of $\alpha_1$- antitrypsin deficiency is between 1 in 2700 to 1 in 5000. Development of emphysema is not invariable in these patients. Although studies have pointed out that there is a progressive decrease in $FEV_1$ in these patients, individuals show large variations. However the life expectancy is greatly decreased if these individuals smoke[59].

**Oxidative stress:**




The effects of oxidative stress[60-62] are

a) Antiprotease inactivation

b) Increased mucus production

c) Proinflammatory gene activation

d) Augmentation of inflammation

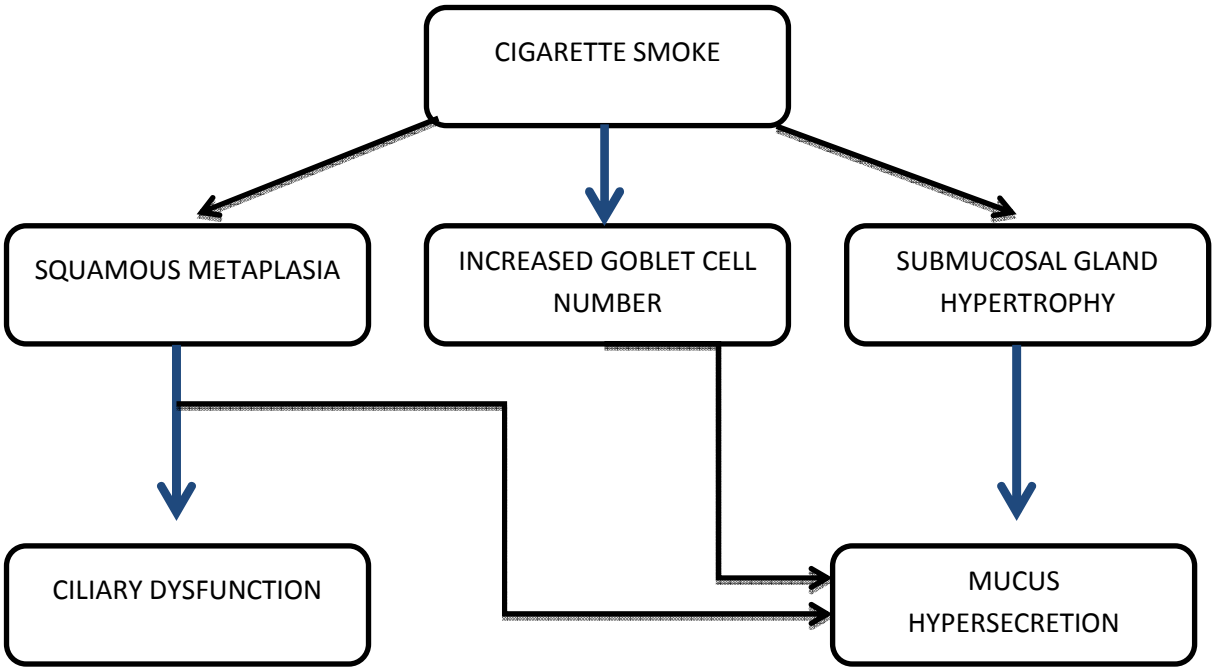
**Pathophysiology:**

The above described pulmonary pathologies produce a number of physiologic abnormalities. They are

a) Mucus hypersecretion
b) Ciliary dysfunction
c) Airflow limitation
d) Hyperinflation
e) Abnormalities in gas exchange
f) Pulmonary hypertension
g) Systemic effects

**Mucus hypersecretion& ciliary dysfunction[63]:**

Mucus hypersecretion culminates in chronic cough which is productive in nature.Airflow limitation is not a sine qua non of chronic bronchitis and similarly chronic productive cough is not present in all patients with COPD.



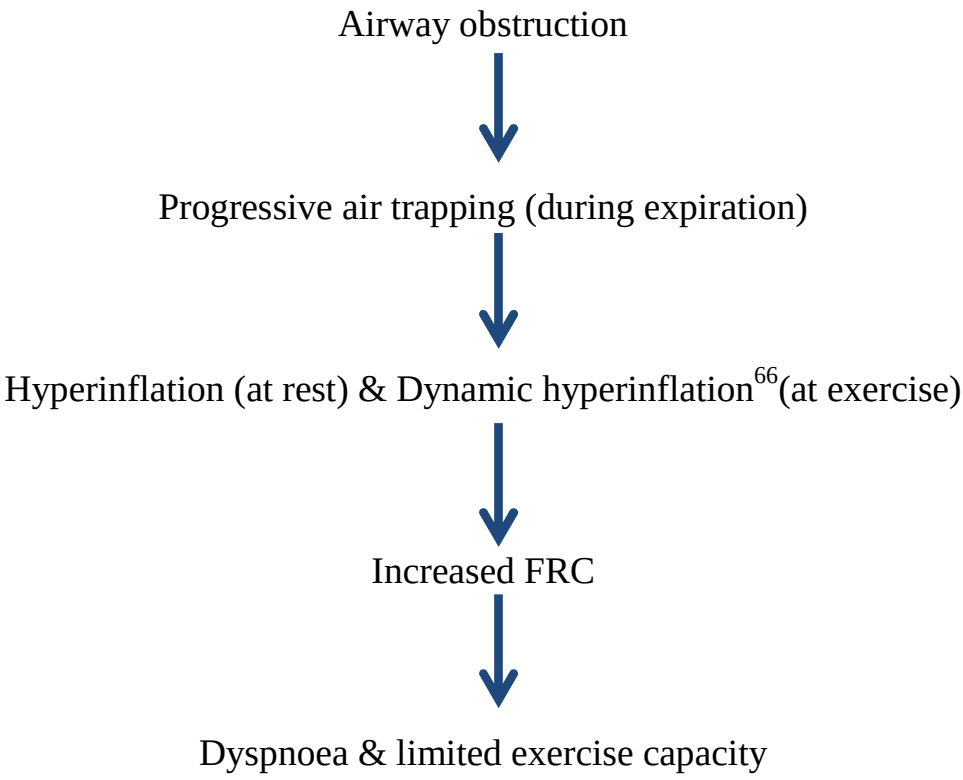

**Airflow limitation & Hyperinflation:**

Decrease in maximum expiratory flow is the characteristic physiological abnormality in COPD[64,65]. Increase in airway resistance and loss of lung elasticity are the major contributors to the subnormal maximum expiratory flow.

In healthy young individuals significant airway closure occurs below functional residual capacity. COPD is characterised by enhanced airway closure at higher lung volumes in the early stages.

| SETTING | CLOSING VOLUME |
|---|---|
| Normal young nonsmoker | 5-10% of VC |
| Old age | 25-35% of VC |
| Young asymptomatic smokers | Increased |

Small conducting airways are the main site of airflow limitation in COPD. Inflammatory exudates and airway narrowing due to remodelling are the major causes for this airflow limitation. Loss of elastic recoil of the lung and alveolar support destruction are other factors that contribute to airflow limitation.




The carbon monoxide transfer factor ($T_LCO$) is mostly reduced in advanced COPD since there is a reduction in ventilated lung volume due to uneven distribution of ventilation.

**Gas exchange abnormalities:**

In COPD, the most important aetiology of impaired gas exchange is the ventilation – perfusion mismatching[67]. Other minor factors that contribute to impaired gas exchange are increased shunt, impaired alveolar- capillary difference to oxygen and alveolar hypoventilation. With disease progression there is worsening of gas exchange. There is uneven distribution of ventilation in COPD patients.

The factors which contribute to reduced blood flow are

a) Local destruction of alveolar wall vessels
b) Hypoxic vasoconstriction
c) Passive vascular obstruction

These factors cause a V/Q mismatch. Impaired function of ventilatory muscles in severe COPD and the V/Q mismatch results in reduced ventilation and $CO_2$ retention.

**Impaired respiratory muscle function:**

In severe COPD there is a reduced respiratory muscle capacity due to muscle weakness[68]. Muscle weakness is caused by lung overinflation and malnutrition. Increase in airway resistance contributes to the increase in load against which the respiratory muscles have to act. Lung overinflation results

in shortening and flattening of the diaphragm thus reducing it's ability to lower pleural pressure.

In normal individuals, expiration is mostly a function of elastic recoil of the lungs during quiet tidal breathing. COPD patients need to use their rib cage muscles and accessory inspiratory muscles for this purpose. This pattern could be further worsened during exertion leading to a paradoxical rib cage motion.

**Pulmonary hypertension:**

Pulmonary arterial hypertension is a late feature of COPD when there is severe hypoxemia and hypercapnia[51,52].

The factors causing PAH are

a) Endothelial dysfunction
b) Pulmonary arterial constriction
c) Destruction of pulmonary capillary bed

PAH causes right ventricular hypertrophy and dysfunction. Corpulmonale due to COPD carries a poor prognosis.

**Systemic effects of COPD:**

Although COPD is primarily a pulmonary disease, severe COPD is punctuated by an array of systemic effects[69,70]. They are

a) Skeletal muscle wasting
b) Cachexia
c) Increased cardiovascular risk
d) Osteoporosis
e) Normocytic normochromic anaemia

These systemic effects could be mediated via reactive oxygen species, IL-6 and TNF α.

**Pathophysiology of COPD exacerbation:**

COPD exacerbations augment the pulmonary inflammation. Neutrophilic inflammation is predominant. There may be an increased number of eosinophils in mild exacerbations. Reactive oxygen species and factors like TNFα, IL-8, $LTB_4$ play a role in these exacerbations.

Airflow limitation is unchanged in mild exacerbations whereas in severe exacerbations are associated with increased V/Q mismatch and fatigue of respiratory muscles[71]. These changes can precipitate respiratory acidosis, respiratory failure, corpulmonale and even death.

**Clinical history:**

**When to suspect COPD?**

COPD should be suspected in any individual > 35 years with complaints of chronic cough, breathlessness, recurrent respiratory infections, sputum production, impaired exercise tolerance with/without history of risk factors. The diagnosis should be confirmed using spirometry.

**Symptoms:**

- Breathlessness ( on exertion +/- wheeze & cough )
- Productive cough ( 50 % )
- Chest pain ( GORD / Ischaemic heart disease/ Exacerbation of COPD )
- Anorexia & weight loss
- Depressed mood
- Other important historical points : fatigue, nocturnal awakening, occupational hazards, ankle swelling, family history

There are scales to assess dyspnoea such as modified Borg scale (min-0;max-10 ) and modified MRC dyspnoea scale ( min-0; max-5 ).

**Clinical examination:**

Physical signs are not specific. They depend on the degree of lung overinflation and airflow limitation. Absence of physical signs does not exclude COPD.

**General examination:**

- Tachypnoea at rest
- Breathing pattern: prolonged expiration, pursed lip breathing
- Use of accessory muscles
- Cyanosis ( advanced disease )
- Flapping tremor ( hypercapnia )
- Muscle wasting
- Tar stained fingers ( smoking )

**Chest Examination:**

- Barrel shaped chest: kyphosis, horizontal ribs, sternal angle prominence, wide subcostal angle, apparent increase of A-P diameter.
- Inspiratory tracheal tug
- Hoover's sign: Inward movement of lower ribs due horizontal position of diaphragm

- Percussion: decreased cardiac and hepatic dullness ( overinflation )
- Breath sounds: increased expiratory phase or diminished breath sounds , wheeze ( both inspiratory and expiratory ), crackles may be heard in lung bases

**Cardiovascular examination:**

- JVP: difficult to localise, prominent 'V' wave ( functional Tricuspid Regurgitation )
- Difficulty in localising apex beat
- Parasternal heave ( PAH )
- Heart sounds: generally soft , Loud $P_2$ ( PAH ) , $S_3$ gallop

**Investigation of respiratory function and exercise capacity:**

In COPD, obstruction to forced expiratory airflow is the most important respiratory disturbance.

**1) Spirometry:**

This is the most vigorous test of airflow limitation in COPD patients[72]. The test is highly effort dependent. Hence maximum effort by the patient must be ensured. The measurements obtained during the test are evaluated by

comparing with appropriate references based on age, sex, height and race. The spirometry criteria for COPD is

1. Post Bronchodilator $FEV_1$ < 80% predicted
2. $FEV_1/FVC$ < 0.7

**2) Reversibility testing[73]:**

This helps to differentiate COPD from asthma. Performing this test is useful for predicting survival in COPD patients since the best predictor of survival is the post bronchodilator $FEV_1$. Although there is no consensus on the standard method of reversibility testing, it can be recorded as a change in $FEV_1$ or peak expiratory flow. A suggested protocol for reversibility testing is

1. 2.5 mg nebulised salbutamol / 400µg salbutamol via metered dose inhaler $\longrightarrow$ $FEV_1$ improves by 15% and 200 ml after 20 minutes.
2. 30 mg prednisolone for 2 weeks $\longrightarrow$ $FEV_1$ improves by 15% and 200 ml.

**DISEASE SEVERITY IN COPD:**

**a) NICE guidelines:**

| **SEVERITY** | **$FEV_1$( % predicted )** | **$FEV_1$/FVC ( % )** |
|---|---|---|
| Stage 1 ( mild ) | 50 - 80 | < 70 |
| Stage 2 ( moderate ) | 30 - 49 | < 70 |
| Stage 3 ( Severe ) | < 30 | < 70 |

**b) GOLD criteria:**

| **SEVERITY** | **$FEV_1$ ( % predicted )** | **$FEV_1$/FVC ( % )** |
|---|---|---|
| Stage 1 ( mild ) | ≥ 80 | < 70 |
| Stage 2 ( moderate ) | 50 - 79 | < 70 |
| Stage 3 ( severe ) | 30 - 49 | < 70 |
| Stage 4 ( very severe ) | < 30 | < 70 or < 50 plus chronic respiratory failure |

**3) Flow volume loops[74]:**

Airflow has been measured using expiratory flows at 75% / 50% of VC ( vital capacity ). These measurements are less reproducible when compared to spirometry and not much of use in clinical settings.

**4) Peak expiratory flow:**

There are two methods to assess peak expiratory flow[75]

a) Handheld peakflow meter
b) Flow volume loops

Peak expiratory flow is particularly useful in asthma whereas in COPD it may underestimate the degree of airflow limitation.

**5) Lung volumes:**

The degree of pulmonary overinflation and air trapping can be assessed by measuring the static lung volumes which include FRC ( functional residual capacity ), RV ( residual volume ), TLC ( total lung capacity ).

The methods by which static lung volumes can be measured are

a) Helium dilution technique – may underestimate lung volumes
b) Body plethysmography – higher lung volume readings than Helium dilution method

**6) Gas transfer for carbon monoxide ($T_L$CO):**

Many COPD patients have a low $T_L$CO. The $T_L$CO and the extent of emphysema are related to each other. Despite the above relationship, emphysema severity cannot be predicted from $T_L$CO. Further, a low $T_L$CO is not specific for emphysema. Single breath technique is the commonly used method for assessing $T_L$CO[76].

**7) Arterial blood gases:**

In COPD patients, arterial blood gases are required for confirming the degree of hypercapnia and hypoxaemia.

Indications for ABG are

a) stable patients with $FEV_1$< 50% predicted
b) clinical evidence of respiratory failure
c) Right heart failure

Pulse oximeter is used for hypoxaemia screening. If $SpO_2$<92, measurement of arterial blood gases becomes necessary.

**8) Exercise testing:**

There is an increase in $O_2$ consumption and production of $CO_2$ during exercise. In 40% of COPD patients exercise capacity is limited by dyspnoea. There are three forms of exercise testing[77,78].

They are

a) Progressive symptom limited exercise
b) Self paced exercise
c) Steady state exercise

**9) Tests of respiratory muscle function:**

Maximum mouth pressures are the routine respiratory muscle function tests in COPD patients. In COPD patients, there is impairment of maximum inspiratory pressures due to hyperinflation & abnormal breathing mechanics. The maximum expiratory pressure is reduced due to muscle weakness.

**10) Sleep studies:**

There is hypoxaemia during sleep , especially REM sleep in COPD patients[79]. Nocturnal hypoxaemia measurements are not of much value unless there is a suscpicionof sleep apnoea syndrome.

**BODE index:**

It is a composite score. With increasing BODE index score there is increased risk of respiratory failure and death.

| **PARAMETER** | **0** | **1** | **2** | **3** |
|---|---|---|---|---|
| $FEV_1$ (% predicted) | ≥65 | 50-64 | 36-49 | ≤35 |
| 6 minute walk distance( m ) | ≥350 | 250-349 | 150-249 | ≤149 |
| MRC scale | 0-1 | 2 | 3 | 4 |
| BMI | ≥21 | ≤21 | | |

**11) Other routine tests:**

- Complete blood count: anaemia of chronic disease, polycythemia

- $\alpha_1$-antitrypsin levels & phenotype: family history of emphysema at young age ; COPD < 45 years of age.

**IMAGING:**

**1) Plain Chest radiography:**

The features in CXR PA view are not specific for COPD. The reliable signs due to emphysema can be discussed under two headings.

They are

a) Lung Overinflation: low flattened diaphragm, increase in retrosternal airspace, obtuse costophrenic angle
b) Vascular changes: number and size of pulmonary vessels are reduced, distortion of vessels, areas of transradiency

**Chest X-ray showing hyperinflated lung fields**

**2) CT chest:**

Assessment of a CT chest in a patient with emphysema reveals

- low attenuation areas without obvious walls or margins

- Vascular tree is attenuated and there is pruning

- Vascular configuration is abnormal

**CT Chest showing Bullae in right lung**


Low attenution is the sign that correlates very well with areas of macroscopic emphysema. The disease severity is usually underestimated in CT scanning. HRCT can distinguish the various morphological variants of emphysema.

Density mask technique is more of a quantitative approach by highlighting pixels in lung field regions between -910 and -1000 HU. This method is useful for assessing macroscopic emphysema. CT lung density is used for quantifying microscopic emphysema. It is expressed on a linear scale in HU. At present, the most sensitive and specific imaging modality for assessing emphysema is CT.

**3) Imaging in patients with PAH / Corpulmonale:**

- CXR: Right ventricle enlargement/hypertrophy

- Echocardiogram: for assessment of PAH

- Right heart catheterization: 'Gold standard' for assessing PAH

**PREVENTION OF COPD:**

It is well known fact that cigarette smoking is the major culprit in causing COPD. Smoking cessation is the single most effective way of reducing the risk of COPD. The five A's in cessation of smoking are **'Ask'**( ask about tobacco use ), **'Advise'** ( advise quitting smoking ), **'Assess'** ( assess willingness to make an attempt ) and **'Assist'** ( assist in quit attempt ), **'Arrange'** ( arrange follow –up ). Many long term smokers develop a withdrawal syndrome which results from nicotine craving. The manifestations of this syndrome are anxiety, increase in appetite, irritability and restlessness. Nicotine gums and nicotine skin patches are useful in these circumstances.

The incidence of COPD can also be reduced by controlling environmental pollution, protection of workers from occupational hazards, alleviating poverty and improving socio economic status of the poor.

## MANAGEMENT OF STABLE COPD:

The ideal goals of COPD treatment are

- Symptom relief
- Improving exercise tolerance
- Health status improvement
- retarding disease progression
- Prevention and treatment of complications
- Prevention and treatment of exacerbations
- Mortality reduction

### 1) Bronchodilators:

They are the cornerstones of COPD treatment with regards to symptom reduction and improving exercise tolerance. In contrast to Bronchial asthma where bronchodilators are highly effective, their effects in COPD are small due to structural changes in airways.

**a) β-Agonists:**

These drugs cause airway smooth muscle relaxation via the β adrenergic receptor – cAMP pathway[80,81]. Inhaled agents are better compared to oral formulations because of higher efficacy at smaller doses and fewer side effects. These drugs can be used for symptomatic relief in COPD patients because of the relatively fast onset of action. Short acting β-agonists are salbutamol, fenoterol and terbutaline. The duration of action of these drugs is around 4-6 hours. Long acting β-agonists are formoterol and salmeterol. These drugs have atleasta 12 hour duration of action. Adverse effects of β-agonist therapy include tachycardia, cardiac rhythm disturbances in susceptible individuals and hypokalemia. These effects are less common with inhalational therapy.

**b) Anticholinergics:**

These drugs act by blocking the muscarinic actions of acetyl choline[82]. The short acting anticholinergics are ipratropium and oxitropium. They are slower than β-agonists (30-60 minutes for peak effect) but have a longer duration of action (6-10 hours).Tiotropium is a longer acting anticholinergic (duration of action – 24 hours) which can be used once daily.

**c) Theophyllines:**

These agents have a modest bronchodilator effect in COPD patients[84]. Their mode of action is still a controversy. They could possibly act as a nonselective phosphodiesterase inhibitor[83]. Theophyllines have a narrow therapeutic index (therapeutic range: 10-20 mg/L). Many patients develop adverse effects within the therapeutic range. Factors such as hypoxaemia, smoking, antibiotics and infection influence theophylline clearance. Thus it is very difficult to titrate theophylline levels in COPD. These drugs can be used as a last resort in patients whose symptoms are adequately controlled by other treatment modalities. Some of the adverse effects of theophyllines are vomiting, abdominal pain, diarrhoea, hypokalemia, cardiac arrhythmias and seizures. Roflumilast and Cilomilast are selective PDE-4 inhibitors that have been recently developed.

**2) Corticosteroids:**

The rationale for using corticosteroids in COPD is the airway inflammation. Their role in COPD is controversial since it is difficult to predict treatment response in patients.

**a) Oral corticosteroids:**

Only 10-20% of stable COPD patients respond to oral corticosteroids. It is difficult to predict which patient will respond. Long term corticosteroid

therapy can cause myopathy which can worsen respiratory function in COPD. Thus oral corticosteroids are not indicated in stable COPD.

**b) Inhaled corticosteroids:**

Majority of the clinical trials using inhaled corticosteroids have failed to show evidence of disease modification in mild to moderate COPD[85,86]. Based on various large scale clinical trials it can be concluded that inhaled corticosteroids have a beneficial effect in patients with $FEV_1$< 50% and those who experience 2 or more exacerbations per year.

Combination therapy (inhaled corticosteroid + long acting β-agonist) appears to be more effective than individual components.

**3) Other agents:**

**a) Vaccines:**

- Influenza vaccine[87]: can reduce mortality due to influenza in COPD patients by 50%. Killed or inactivated virus vaccines are recommended. The vaccine is given once a year.
- Pneumococcal vaccine[88]: recommended in COPD patients older than 65 years. It reduces the incidence of community acquired pneumonia in patients with very severe disease.

**b) Antibiotics:**

There is no conclusive evidence for the use of continuous prophylactic antibiotics in COPD.

**c) Mucolytic agents:**

Regular use of mucolytics has some effect in reducing the frequency of exacerbations. Carbocisteine and mecysteine hydrochloride are the mucolytic agents used in COPD[89]. These agents can be used in patients who experience frequent exacerbations and those who have difficulty in expectorating sputum. At present, N-Acetylcysteine is not recommended in COPD treatment.

**d) Antitussives:**

Although cough can be a troublesome symptom in some COPD patients, regular use of antitussives is not recommended since cough has a protective role in this setting.

**4) Oxygen therapy:**

Domiciliary oxygen therapy is the only treatment by which long term prognosis is improved in COPD patients[90]. The two major trials conducted on domiciliary oxygen therapy are the NOTT (Nocturnal Oxygen Therapy Trial) in the USA and the MRC trial (Medical Research Council) in the UK. In the MRC trial there was an improvement in five year survival rates from 25 to 41% among those using oxygen for 15 hours/day (compared with no oxygen). Continuous oxygen therapy (mean use – 17.5 hours/day) improved survival whereas use of 12 hours/day was of no use according to the NOTT. Long term oxygen therapy did not halt or slow the decline in $FEV_1$even though $FEV_1$ is the strongest predictor of survival in COPD.

The three forms of domiciliary oxygen therapy are

a) Long term controlled $O_2$ therapy:

- given via nasal prongs or masks ;transtracheal route ( if there is refractory hypoxaemia )

- 15 hours/day

- useful in patients with chronic respiratory failure

b) Ambulatory $O_2$ therapy ( for exercise related hypoxaemia )

c) Short burst $O_2$ therapy ( palliative treatment useful in the temporary relief of dyspnoea )

**Oxygen during air travel:**

- Who are safe to fly without supplemental $O_2$?

  Patients with $SpO_2$> 95% and resting $PaO_2$ ( at sea level ) > 70 mmHg.

- Who require oxygen while flying?

  Patients on home $O_2$ therapy

  $SpO_2$< 92%

- If 95 > $SpO_2$< 92?

  These patients are vulnerable to desaturation at high altitudes. They should be offered a 'Hypoxic challenge test'. If the $PaO_2$ remains more than 55 mmHg, $O_2$ is not usually required. If $PaO_2$ falls below 50 mmHg, an in-flight $O_2$of 2 litres/min is advised. The remaining cases are managed according to clinical judgement.

**5) Ventilatory support:**

NIPPV ( noninvasive positive pressure ventilation ) is not of much use in stable COPD patients and in those with chronic respiratory failure.

Combination of NIPPV with long term $O_2$ therapy could be useful in select patients who experience prolonged daytime hypercapnia.

**6) Pulmonary rehabilitation:**

Pulmonary rehabilitation is defined as *"a multidisciplinary programme of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy"*. This is very useful in patients with moderate to severe COPD.

The components of pulmonary rehabilitation are

a) Exercise training
b) Education
c) Psychosocial and behavioural intervention
d) Nutritional therapy

The benefits of pulmonary rehabilitation[91] are

a) Reduction of intensity of dyspnoea on exertion
b) Improvement in exercise tolerance
c) Improvement in quality of life
d) Reduction in the number of admission days
e) Psychological improvement

## MANAGEMENT OF ACUTE COPD EXACERBATIONS:

Sustained worsening of symptoms is a characteristic of COPD exacerbations. Frequent exacerbations lead to an accelerated decline in lung function.

### Assessment of severity:

The severity of COPD exacerbation can be assessed by comparing previous medical history with the presenting symptoms. Spirometry is inaccurate in this setting. Pulse oximeter is useful to assesss the need for supplemental $O_2$. Chest X ray should be obtained to rule out alternative diagnosis such as bronchopneumonia, pneumothorax and pulmonary oedema.

### Oxygen therapy:

This forms a vital part in the management of severe COPD exacerbations. The aims of $O_2$ therapy is to maintain a $PaO_2$>60 mmHg and $SpO_2$> 90 mmHg. Blood gases are checked 30-60 minutes after initiating $O_2$ therapy to assess the adequacy of treatment.

**Bronchodilators:**

Nebulized bronchodilators should be given at 4-6 hour intervals. β-agonists such as salbutamol 2.5-5 mg or an anticholinergic such as ipratropium 0.5 mg are used.

Intravenous methylxanthines can be used if the patient does not respond to bronchodilators. Aminophylline is used as a loading dose of 6 mg/kg followed by maintenance of 0.5 mg/kg/hour.

**Antibiotics[92]:**

COPD exacerbations are commonly precipitated by infections. The recommended broad spectrum antibiotics are amoxicillin (250 mg TDS PO) or clarithromycin (250-500 mg BD PO) in case of penicillin allergy.

**Respiratory stimulants:**

The role of doxapram in COPD[93] has diminished since the introduction of non invasive ventilation. If non invasive ventilation is not available or is contraindicated, intravenous doxapram infusion can be used. The usefulness of doxapram is limited by its adverse effects such as tachycardia and hallucinations.

**Diuretics:**

These drugs should be carefully titrated to avoid overdiuresis which can result in cardiac output reduction by reducing right ventricular end diastolic volume.

**Anticoagulants:**

In patients with severe COPD, pulmonary emboli go under recognized[94]. CT pulmonary angiogram is the imaging modality of choice in this setting since V/Q scans can lead on to false positive results. Prophylactic LMW heparin is given subcutaneously in COPD exacerbations, particularly if there is respiratory failure.

**Physiotherapy:**

Physiotherapy has little or no role in COPD exacerbations.

## SURGICAL TREATMENT OF COPD:

### Bullous emphysema:

The various presentations of bullae are

- Chance finding in CXR
- Pneumothorax
- Infection with consolidation

The usual presenting symptom is exertional dyspnoea. Surgical obliteration is the only possible treatment for large bulla[95]. The aims of surgery are

- Bullous space obliteration
- To restore lung elasticity

Some of the techniques used are intracavitary drainage, plication, marsupialization and excision. Most procedures are done via conventional lateral thoracotomy.Best results are achieved in young patients with a large bulla and normal surrounding lung.

### Lung volume reduction surgery:

The rationale for this procedure is reduction in the volume of emphysematous lung. The NETT (National Emphysema Treatment Trial

)compared medical treatment with LVRS in emphysema patients. This study showed superior survival rates in the LVRS arm compared to the medical treatment arm.

**Lung Transplantation:**

This procedure can be performed in carefully selected very severe COPD patients. Although it improves quality of life and functional capacity, there is no survival benefit beyond 2 years in endstage emphysema.

## THE TESTES:

The testes are paired endocrine organs in males. They are the major source of testosterone. The shape of adult testis is prolate spheroid. The mean volume of testis is about 18.6 +/- 4.8 ml.

The two major components of testis are

- Leydig cells (Interstitial cells): This is the main endocrine component of the testis. Testosterone is the principal secretory product of these cells. Testosterone is responsible for embryonic differentiation along male lines, secondary sexual character development in males and maintenance of libido and potency.

- Seminiferous tubules: They form the testis bulk. These tubules produce spermatozoa.

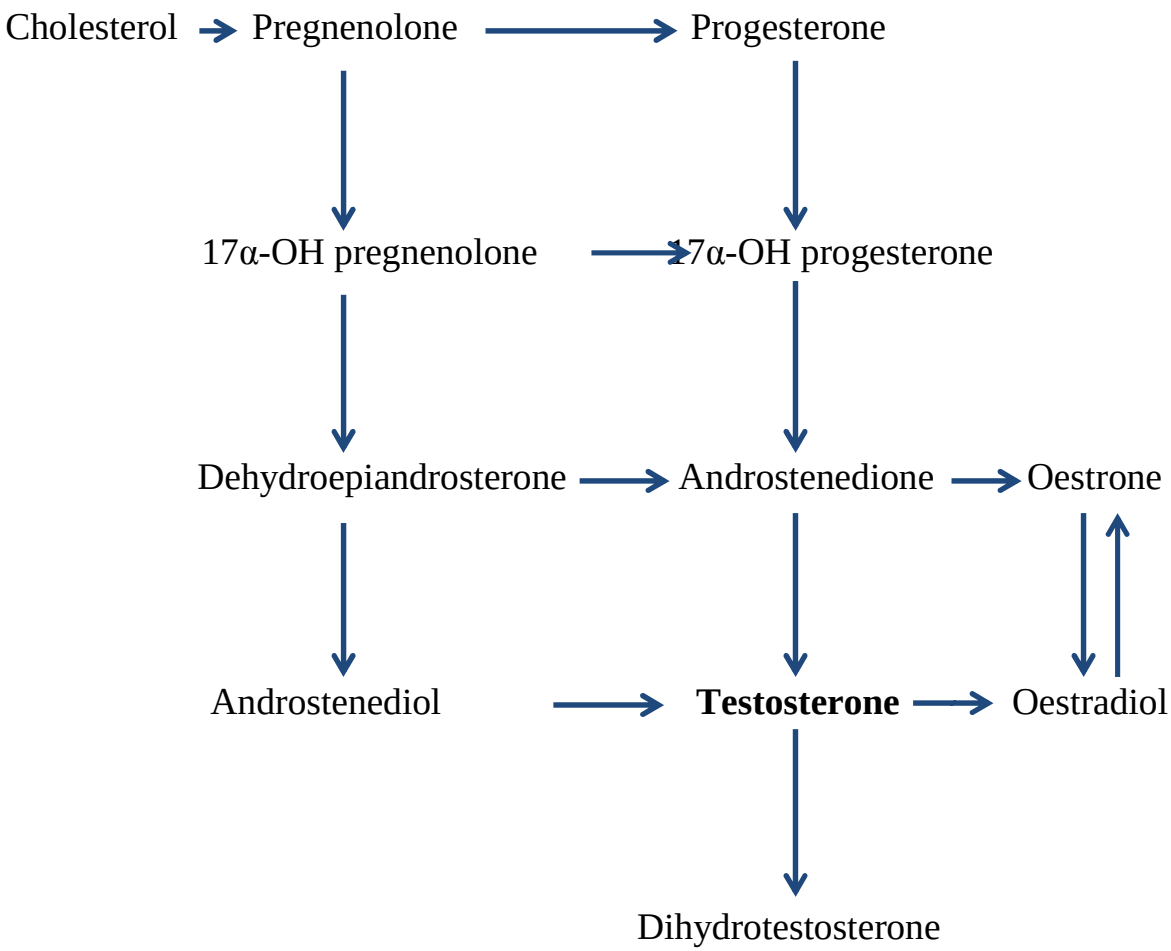
**Gonadal Steroids:**

The most important steroids associated with male reproductive function are

a) Testosterone
b) Dihydrotestosterone
c) Oestradiol

| **HORMONE** | **SECRETION FROM TESTIS** | **SECRETION FROM ADRENALS** | **PRECURSOR CONVERSION IN PERIPHERIES** |
|---|---|---|---|
| Testosterone | 95% | <1% | <5% |
| Dihydrotestosterone | <20% | <1% | 80% |
| Oestradiol | <20% | <1% | 80% |

**Testosterone biosynthesis:**




**Testosterone metabolism:**

The major site of testosterone metabolism is the liver. Testosterone is converted into etiocholanolone and androsterone. These metabolites are conjugated with sulphuric acid and glucuronic acid and undergo urinary excretion as 17-ketosteroids. Some amount of the hormone is converted into dihydrotestosterone.

**Control of testosterone secretion:**

**The hypothalamic – pituitary – leydig cell axis:**

GnRH (Gonadotropin releasing hormone) is a decapeptide secreted from the hypothalamus in a pulsatile manner (every 30-120 min). It acts on the pituitary gonadotrophs and stimulates LH (Luteinizing Hormone) release mainly and FSH (Follicle Stimulating Hormone) to a lesser extent. LH enters the general circulation and reaches the testis. It acts on the leydig cells resulting in cAMP generation and StAR synthesis. The end result is increased testosterone synthesis. The androgens have negative feedback control on moth hypothalamus and pituitary.

**Male Hypogonadism:**

Male hypogonadism is a " *clinical syndrome that results from a failure of the testis to produce adequate amounts of testosterone; this is almost always associated with impaired sperm production or with an isolated impairment of sperm production or function with normal testosterone production*".

**Classification of male hypogonadism:**

1) Hypothalmic pituitary disorders:
    - Panhypopituitarism
    - Isolated FSH deficiency
    - Isolated LH deficiency
    - FSH & LH deficiency ( Kallmann syndrome, Prader-Willi syndrome, Lowe Syndrome, Mobius syndrome, Cerebellar ataxia, Lawrence – Moon – Biedl syndrome )
    - Hyperprolactinaemia
    - Biologically inactive LH
2) Gonadal disorders:
    - Chromosomal defects: XX male, XX/XXY, XY/XXY, XXXY, XXXXY, XXYY, XYY
    - Klinefelter syndrome
    - Vanishing testes syndrome
    - Cryptorchidism
    - Leydig cell aplasia
    - Noonan syndrome
    - Adult seminiferous tubule failure
    - Myotonic dystrophy
    - Androgen biosynthesis defects

- Adult leydig cell failure

3) Defects in androgen action:

- Testicular feminization syndrome
- Incomplete androgen insensitivity

**Clinical features of adult hypogonadism:**

Male hypogonadism is diagnosed in individuals with clinical features of androgen deficiency and low serum levels of testosterone. Prevalence of low testosterone levels are higher than symptomatic androgen deficiency among middle to old aged males. The predominant symptoms of androgen deficiency are decreased libido, erectile dysfunction, fatigue, depressed mood and sleep disturbances. The risk of diabetes mellitus and cardiovascular events are also increased in this setting. Hypogonadism is diagnosed in men who exhibit clinical features of androgen deficiency by demonstrating consistently low serum levels of serum testosterone[103].

**Testosterone measurements:**

Serum testosterone levels show both assay and biological variability. There must be consistent and unequivocal evidence of low serum testosterone levels for the diagnosis of androgen deficiency. The exact thresholdof serum

testosterone level at which symptoms of androgen deficiency occur are not known. However a level of 280-300 ng/dl can be used when testing done by an accurate and reliable assay.

**Variability in serum testosterone levels:**

Circadian and ultradian variations are exhibited by serum testosterone levels. Peaking of circadian variation occurs at about 8 am. This excursion is blunted in old age (approx. 60 ng/dl) when compared to younger individuals (approx. 140 ng/dl). Further, the testosterone level is 20-25% lower at 4 pm when compared to 8 am in younger individuals. In older men, the levels are approximately 10% lower at 4 pm when compared to 8 am. Considering these variations, testosterone levels are best measured in the morning.

Day to day variation in testosterone levels are also significant. In a study, 30% of the men who had initial testosterone levels less than 300 ng/dl had normal testosterone levels on subsequent testing. These factors emphasize the importance of repeat measurements of serum testosterone levels.

**Total testosterone assays:**

These assays are generally readily available. The recommended initial measurement of androgen deficiency is total testosterone levels. There are wide variations among various laboratories due to inadequate quality control. Liquid chromatography - tandem mass spectrometry is an accurate method of measuring testosterone. A variety of clinical settings such as diabetes mellitus, chronic kidney disease, and HIV infection, moderate to severe lung disease are associated with low testosterone levels[99]. Total testosterone levels are influenced by SHBG (Sex Hormone Binding Globulin) levels since about 30-40% of testosterone in circulation is bound to SHBG.

| **Low SHBG concentration** | **High SHBG concentration** |
|---|---|
| - Moderate obesity<br>- Type 2 diabetes mellitus<br>- Acromegaly<br>- Hypothyroidism<br>- Nephrotic syndrome<br>- Glucocorticoids, androgens & Progestins<br>- Familial SHBG deficiency | - Aging<br>- Oestrogens<br>- HIV<br>- Anticonvulsants<br>- Hyperthyroidism<br>- Cirrhosis & Hepatitis |

Conditions that decrease SHBG levels tend to decrease total testosterone levels. In these conditions, free testosterone levels should be measured. Equilibrium dialysis or centrifugal ultrafiltration is the gold standard method for measuring free testosterone levels. Automated platform – based analogimmunoassays for free testosterone measurement is affected by changes in SHBG. Hence they are inaccurate and not useful clinical settings.

Testosterone levels can be suppressed transiently by certain conditions such as critical illness, high dose glucocorticoids and CNS- active drugs. These factors should be taken into consideration while interpreting serum testosterone levels.

**Testosterone replacement therapy:**

A variety of preparations are available for treating androgen deficiency

a) Sublingual or oral : Methyltestosterone, Oxymetholone, Fluoxymesterone
b) Oral: Testosterone propionate
c) Intramuscular: Testosterone enanthate, Testosterone cypionate, Testosterone undecanoate
d) Subcutaneous implantation: Testosterone pellets

e) Transdermal: Testosterone patch

f) Local application: 1% testosterone gel, buccal preparation ( Striant )

These preparations are contraindicated in prostatic carcinoma.

**Adverse effects:**

- Intrahepatic cholestasis with methyltestosterone and fluoxymesterone
- Premature epiphyseal fusion
- Hypertension, CCF
- Erythrocytosis
- Oligospermia
- Priapism
- Sleep apnoea
- Acne
- Aggressive behaviour
- Decreased HDL levels

**Testosterone levels in COPD:**

Low serum testosterone levels are common in male COPD patients[97,98,101,104-108]. The prevalence of low testosterone levels vary widely according to the population studied. Low or low – normal gonadotropin

levels are found in 75% of the male COPD patients with low testosterone levels[96]. The remaining patients have primary hypogonadism with elevated gonadotropin levels[100].

The coexistent features that are common in hypogonadal male COPD patients are muscle wasting & cachexia, glucocorticoid usage and hypoxia. Hypoxia can suppress both gonadotropin and testosterone secretion.

Testosterone replacement therapy has been tried in male COPD patients with low testosterone levels. This treatment strategy improved lean body mass but fails to improve endurance and quality of life[102].

# METHODOLOGY

# METHODOLOGY

**Setting:**

This study was done at the Institute of Internal Medicine, Madras Medical College. All patients were either already inpatients or were admitted for conducting the study.

**Study design:**

Single center cross sectional study

**Study period:**

July - September 2014

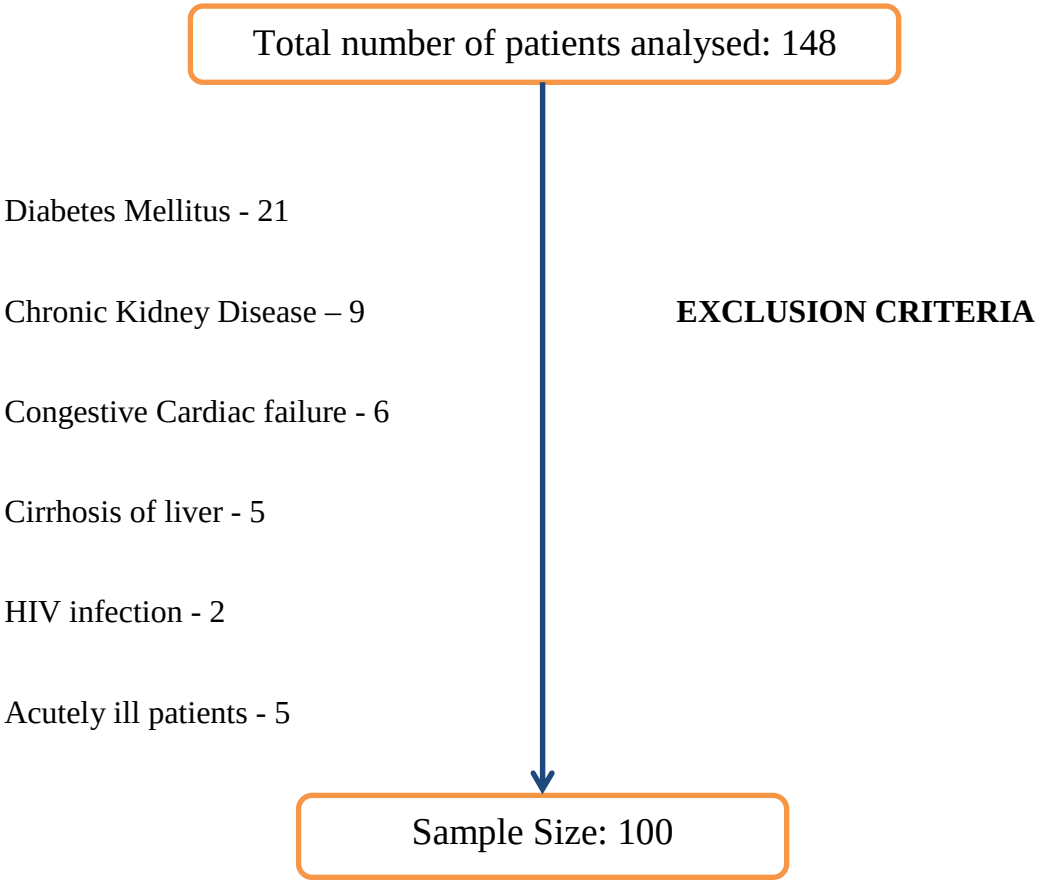
**Collaborating departments:**

The Institute of Thoracic Medicine was crucial to this study. This department served as a source of a substantial proportion of cases. It also was the site for doing spirometry for the patients enrolled in the study.

Various other departments helped in doing this study. The Cardiology department helped in performing echocardiogram for the patients. The services of Barnard Institute of Radiology were utilized for imaging purposes. The Institute of Biochemistry played an important role by performing various biochemical tests.

**Selection of subjects:**

Male COPD patients of ≥40 years of age with disease duration ≥ 5 years were analysed. Out of the 148 patients analysed, 48 patients were excluded from the study according to the proposed exclusion criteria.




**Inclusion Criteria:**

1) Male COPD patients
2) Age ≥ 40 years
3) Duration of disease ≥ 5 years

**Exclusion Criteria:**

1) Diabetes Mellitus
2) Chronic Kidney Disease
3) Congestive Cardiac Failure
4) Cirrhosis
5) Obesity
6) Thyrotoxicosis
7) HIV infection
8) Acutely ill patients

**Details of study subjects:**

**Demography:**

The subjects who underwent this study were mostly from the northern districts of Tamil Nadu and the neighbouring state Andhra Pradesh.

Study details:

The patients who were analysed prior to enrolment underwent a thorough history taking and clinical assessment. They were either inpatients already or were admitted for further assessment.

They underwent various biochemical tests and imaging studies. Exclusion criteria were strictly applied in this study.

1) Diabetes Mellitus: Fasting Blood Sugar ≥ 126 mg/dl or Post prandial Blood Sugar ≥ 200 mg/dl or both
2) Chronic Kidney Disease: Ultrasonographic evidence of small echogenic kidneys or Calculated Glomerular Filtration rate as per Cockroft – Gault formula < 90 ml/min/1.73 $m^2$ or both with or without proteinuria
3) Congestive cardiac failure: Clinical evidence of volume overload status with echocardiographic evidence of biventricular dysfunction
4) Cirrhosis: Ultrasonographic evidence of contracted liver with altered echoes with or without clinical evidence of volume overload status/Liver cell failure
5) Obesity: Body mass index ≥ 30 $Kg/m^2$
6) Thyrotoxicosis: Clinical features of Hyperthyroidism or laboratory evidence of hyperthyroidism( Serum free $T_4$> 1.86 ng/dl and Serum TSH> 4 mU/L )
7) HIV infection: Positive for HIV-1 or HIV-2 ELISA
8) Acutely ill patients: COPD patients with acute exacerbation requiring ventilator support

After exclusion of the above mentioned patients, the remaining patients were questioned regarding symptoms suggestive of hypogonadism and they

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# OBSERVATION

## OBSERVATION AND RESULTS:

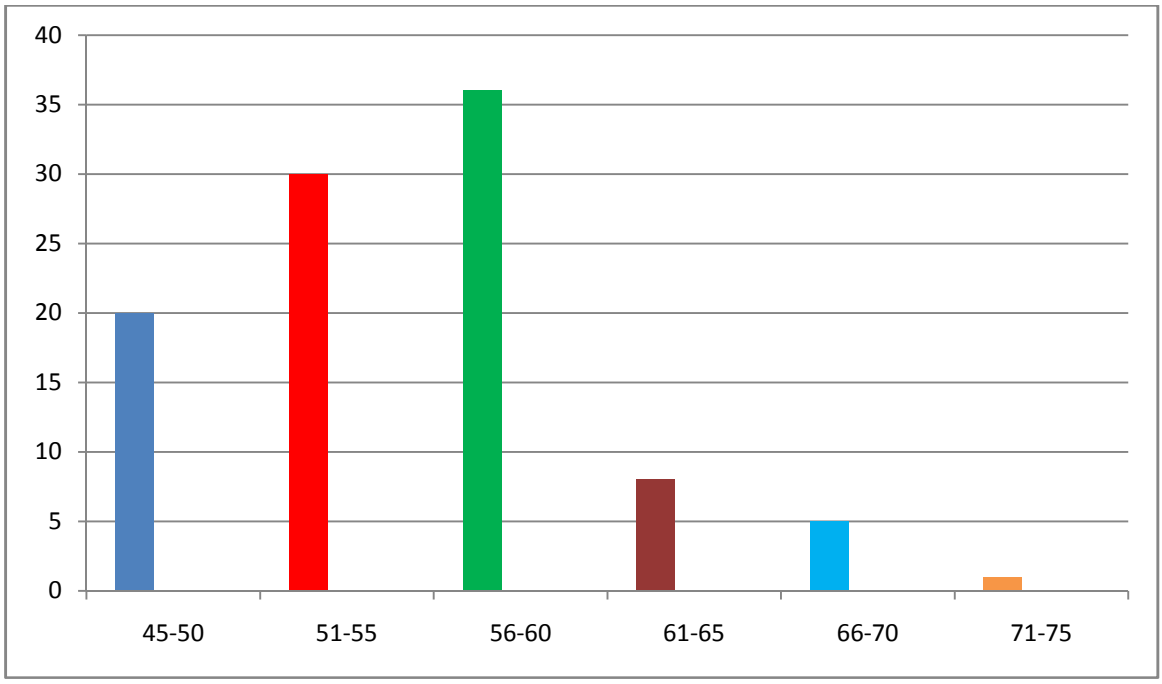
The study group included 100 patients. Low testosterone levels were found in 34 of the 100 male COPD patients studied.

### 1) Age Distribution:

| AGE GROUP ( YEARS ) | NO. OF PATIENTS | PERCENTAGE |
|---|---|---|
| 45-50 | 20 | 20 |
| 51-55 | 30 | 30 |
| 56-60 | 36 | 36 |
| 61-65 | 8 | 8 |
| 66-70 | 5 | 5 |
| 71-75 | 1 | 1 |

The above table depicts the age distribution of the patients enrolled in this study. All the patients were more than or equal to 45 years of age. The age interval 56-60 had the highest number of patients (36).

## Age distribution

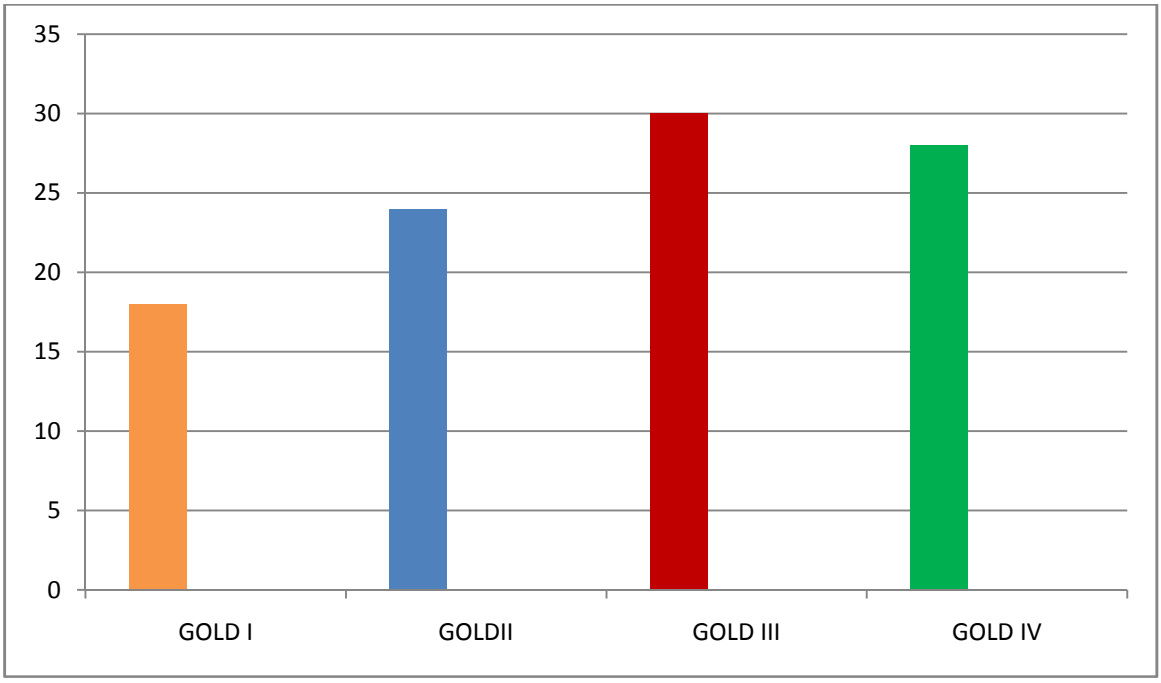


## 2) Number of patients in each GOLD stage:

| GOLD STAGE | NO. OF PATIENTS ( % ) |
|---|---|
| I | 18(18) |
| II | 24(24) |
| III | 30(30) |
| IV | 28(28) |

The above table shows the number of patients in each GOLD stage. There is a fairly even distribution of patients across all stages with stage III housing the highest number of patients.

**Patient distribution across GOLD stages**



**3) GOLD stage distribution in the age interval 45-50 years:**

| PARAMETER | GOLD STAGE | | | |
|---|---|---|---|---|
| | I | II | III | IV |
| Count | 8 | 7 | 4 | 1 |
| % Within age interval | 40 | 35 | 20 | 5 |
| %Within GOLD stage | 44.4 | 29.2 | 13.3 | 3.6 |

Majority of the patients in the age interval of 45-50 years in this study fell within GOLD stage I. Also, patients in this age interval formed a major part of the total GOLD I population in this study.

**4) GOLD stage distribution in age interval 51-55 years:**

| PARAMETER | GOLD STAGE | | | |
|---|---|---|---|---|
| | I | II | III | IV |
| Count | 5 | 9 | 8 | 8 |
| % Within age interval | 16.7 | 30 | 26.7 | 26.7 |
| % Within GOLD stage | 27.8 | 37.5 | 26.7 | 28.6 |

In this age interval, the patients are more or less evenly spread across all GOLD stages with a slight tilt towards GOLD stage II.

**5) GOLD stage distribution in age interval 56-60 years:**

| **PARAMETER** | **GOLD STAGE** | | | |
|---|---|---|---|---|
| | I | II | III | IV |
| Count | 4 | 6 | 11 | 15 |
| % Within age interval | 11.1 | 16.7 | 30.6 | 41.7 |
| % Within GOLD stage | 22.2 | 25 | 36.7 | 53.6 |

More than half of the cases in this age interval belonged to GOLD stage IV. Conversely, more than half of the GOLD stage IV patients in this study were from this age interval.

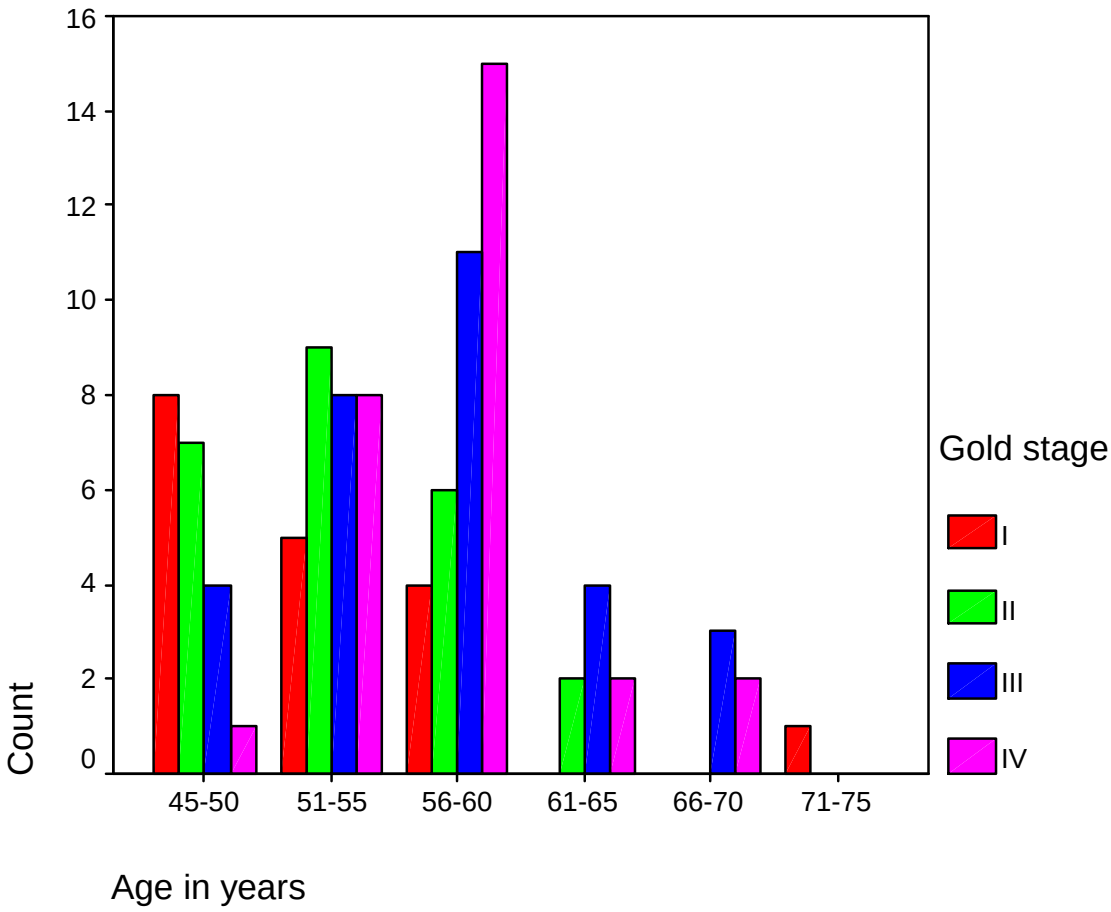
**6) GOLD stage distribution in age interval 61-65 years:**

In this age interval, there were only eight patients. Half of the patients came under GOLD stage III in this age interval.

| **PARAMETER** | **GOLD STAGE** | | | |
|---|---|---|---|---|
| | I | II | III | IV |
| Count | 0 | 2 | 4 | 2 |
| % Within age interval | 0 | 25 | 50 | 25 |
| % Within GOLD stage | 0 | 8.3 | 13.3 | 7.1 |

The remaining two age intervals of 66-70 and 71-75 had only five and one patient respectively. Half the patients of these two age intervals combined belonged to GOLD stage III.

## AGE DISTRIBUTION ACROSS GOLD STAGES



**7) Serum Testosterone levels in the age interval 45-50 years:**

| **PARAMETER** | **SERUM TESTOSTERONE** | |
|---|---|---|
| | < 280 ng/dl | ≥ 280ng/dl |
| Count | 2 | 18 |
| % Within age interval | 10 | 90 |
| % Within serum testosterone levels | 5.9 | 27.3 |

In this age interval 90% of patients had normal testosterone levels. Individuals in this age interval made up more than one fourth of the individuals in this study with normal testosterone levels.

**8) Serum Testosterone levels in the age interval 51-55 years:**

| **PARAMETER** | **SERUM TESTOSTERONE** | |
|---|---|---|
| | <280 ng/dl | ≥ 280 ng/dl |
| Count | 13 | 17 |
| % Within age interval | 43.3 | 56.7 |
| % Within Serum testosterone levels | 38.2 | 25.8 |

Patients in this age interval make up more than one third of the patients with low testosterone levels. The prevalence of low testosterone levels in this age interval is just above 40% in this study.

**9) Serum Testosterone levels in the age interval 56-60 years:**

| **PARAMETER** | **SERUM TESTOSTERONE** | |
|---|---|---|
| | < 280 ng/dl | ≥ 280 ng/dl |
| Count | 15 | 21 |
| % Within age interval | 41.7 | 58.3 |
| % Within serum testosterone levels | 44.1 | 31.8 |

Patients in this age interval make the highest contribution to the group with low testosterone levels in this study.

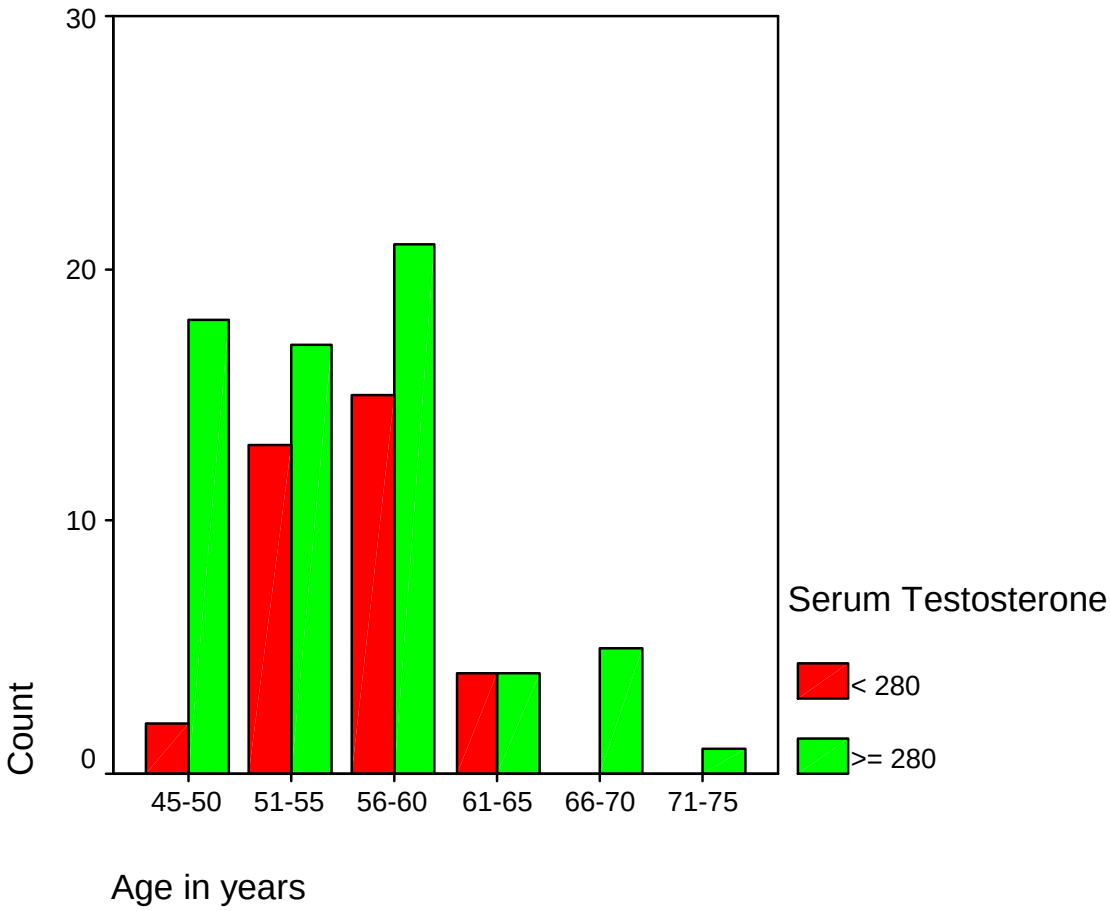
**10) Serum Testosterone levels in the age interval 61-65 years:**

Half of the patients in this age interval fell in each of the two testosterone groups.

Surprisingly, the remaining patients in the age intervals 66-70 and 71-75 fell into the normal testosterone group. Since they are only six in number, no conclusion can be drawn from this data.

| **PARAMETER** | **SERUM TESTOSTERONE** | |
|---|---|---|
| | < 280 ng/dl | ≥ 280 ng/dl |
| Count | 4 | 4 |
| % Within age interval | 50 | 50 |
| % Within serum testosterone levels | 11.8 | 6.1 |

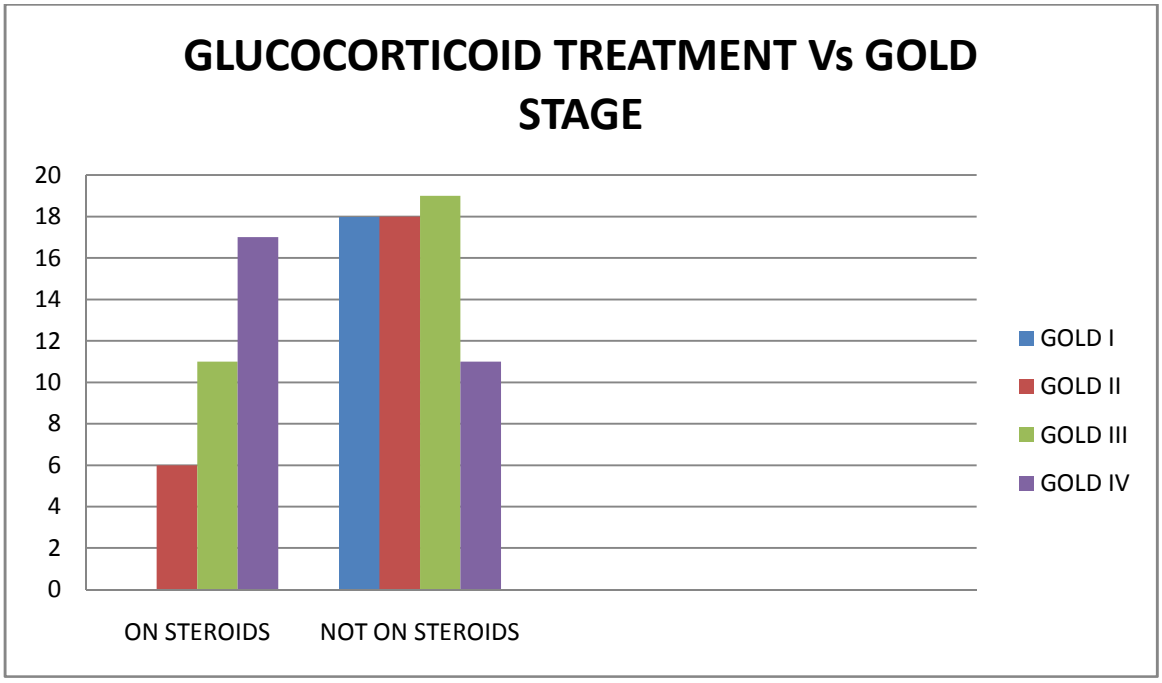
## AGE AND TESTOSTERONE LEVEL



**11) Comparison of glucocorticoid treatment and GOLD stage:**

| **GLUCOCORTICOID TREATMENT** | **PARAMETER** | **GOLD STAGE** | | | |
|---|---|---|---|---|---|
| | | I | II | III | IV |
| Present | Count | 0 | 6 | 11 | 17 |
| | % Within GOLD stage | 0 | 25 | 36.7 | 60.7 |
| Absent | Count | 18 | 18 | 19 | 11 |
| | % Within GOLD stage | 100 | 75 | 63.3 | 39.3 |

Among the 100 patients enrolled in the study 34 patients were on long term glucocorticoid therapy. Patients who had received inhalational or intravenous steroids only during exacerbations and not on regular treatment were not considered as patients on glucocorticoid treatment. Majority of the patients on long term glucocorticoid therapy were within GOLD stage IV. All the patients in GOLD stage I were not on corticosteroid therapy.

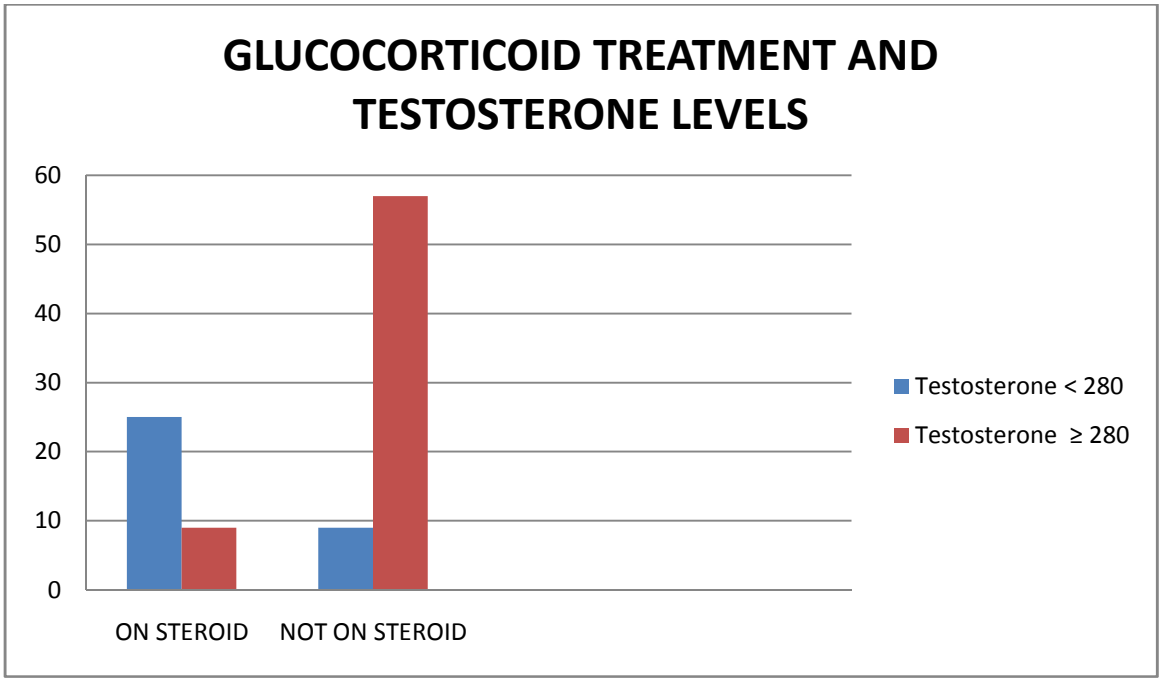

GLUCOCORTICOID TREATMENT Vs GOLD STAGE
20
18
16
14
12
10
8
6
4
2
0
ON STEROIDS
NOT ON STEROIDS
GOLD I
GOLD II
GOLD III
GOLD IV

**12) Comparison of glucocorticoid treatment and serum testosterone levels:**

| **GLUCOCORTICOID TREATMENT** | **PARAMETER** | **SERUM TESTOSTERONE** | |
|---|---|---|---|
| | | <280 ng/dl | ≥ 280 ng/dl |
| Present | Count | 25 | 9 |
| | % in patients on treatment | 73.5 | 26.5 |
| Absent | Count | 9 | 57 |
| | % inpatients not on treatment | 13.6 | 86.4 |

Pearson Chi-Square test: p value: < 0.001( highly significant )

Approximately three fourth of the patients on long term glucocorticoid treatment had low testosterone levels in this study. The association between long term glucocorticoid treatment and low testosterone levels is highly significant as per the calculated p value.

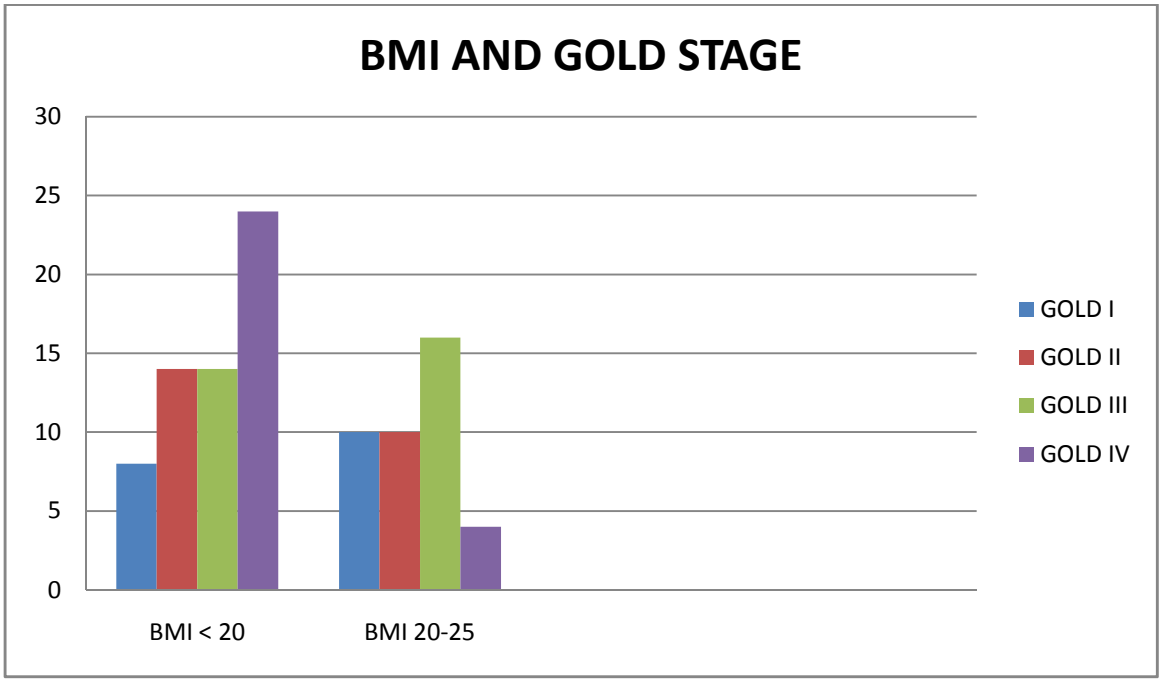

GLUCOCORTICOID TREATMENT AND TESTOSTERONE LEVELS
60
50
40
30
20
10
0
ON STEROID
NOT ON STEROID
Testosterone < 280
Testosterone ≥ 280

**13) Comparison between body mass index and GOLD stage:**

| **BMI ( Kg/m$^2$)** | **PARAMETER** | **GOLD STAGE** | | | |
|---|---|---|---|---|---|
| | | I | II | III | IV |
| < 20 | Count | 8 | 14 | 14 | 24 |
| | % Within low BMI group | 13.3 | 23.3 | 23.3 | 40 |
| 20-25 | Count | 10 | 10 | 16 | 4 |
| | % Within low BMI group | 25 | 25 | 40 | 10 |

Pearson's Chi-Square test: p value: 0.008 (< 0.01, highly significant)

Of the 100 enrolled patients, 60 had low BMI. Among the patients with low BMI, 40% fell within GOLD stage IV. Among the 40 patients with normal BMI, majority (40%) fell within GOLD stage III.

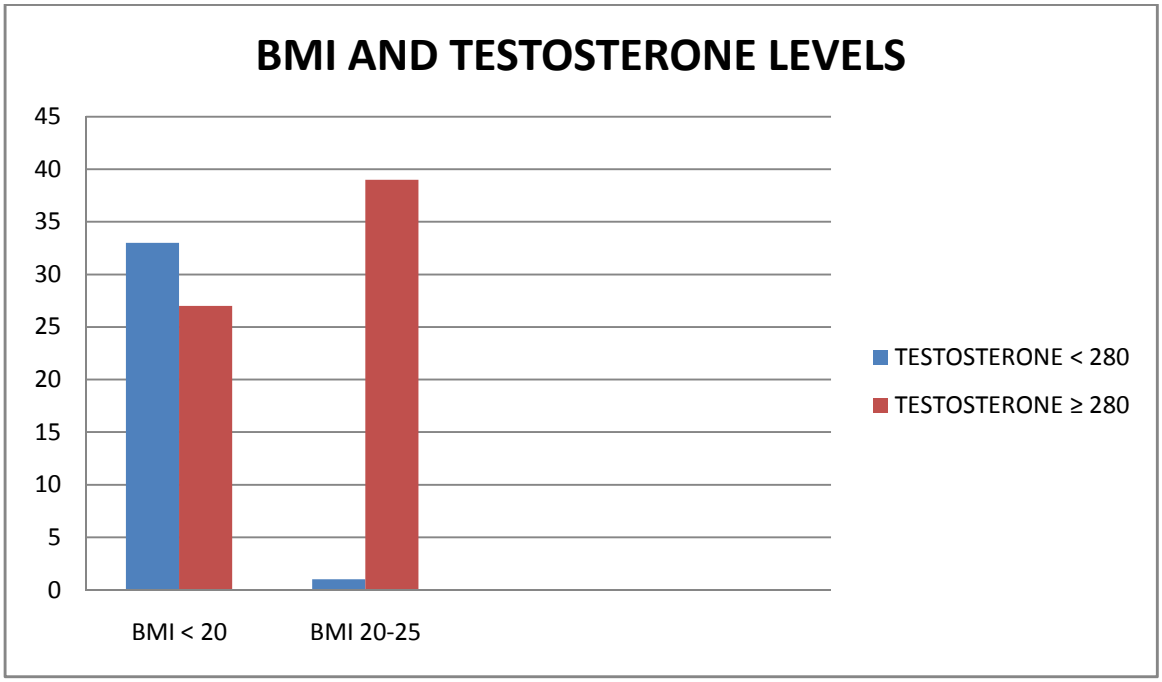

BMI AND GOLD STAGE
30
25
20
15
10
5
0
BMI < 20
BMI 20-25
GOLD I
GOLD II
GOLD III
GOLD IV

**14) Comparison between body mass index and serum testosterone:**

| **BMI ( KG/M$^2$)** | **PARAMETER** | **SERUM TESTOSTERONE** | |
|---|---|---|---|
| | | < 280 ng/dl | ≥ 280 ng/dl |
| < 20 | Count | 33 | 27 |
| | % Within low BMI | 55 | 45 |
| 20-25 | Count | 1 | 39 |
| | % Within normal BMI | 2.5 | 97.5 |

Pearson Chi-Square test: p value: < 0.001 (highly significant)

More than half of the patients with low BMI had low testosterone levels. The p value for this association is < 0.001 and is highly significant. However, majority of the patients with normal BMI had normal testosterone levels.

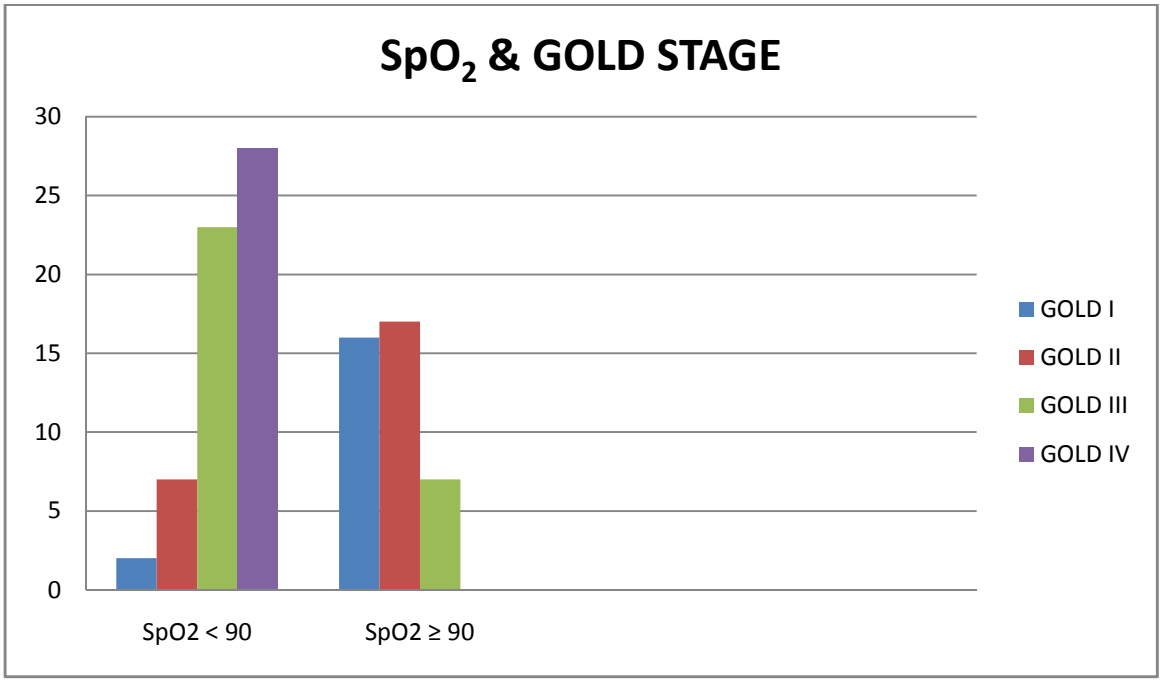

BMI AND TESTOSTERONE LEVELS
45
40
35
30
25
20
15
10
5
0
BMI < 20
BMI 20-25
TESTOSTERONE < 280
TESTOSTERONE ≥ 280

**15) Comparison between $SpO_2$ and GOLD stage:**

| **$SpO_2$** | **PARAMETER** | **GOLD STAGE** | | | |
|---|---|---|---|---|---|
| | | I | II | III | IV |
| < 90 | Count | 2 | 7 | 23 | 28 |
| | % within low $SpO_2$ group | 3.3 | 11.7 | 38.3 | 46.7 |
| ≥ 90 | Count | 16 | 17 | 7 | 0 |
| | % within normal $SpO_2$ group | 40 | 42.5 | 17.5 | 0 |

Pearson Chi-Square test: p value: < 0.001 (highly significant)

Among the enrolled patients, 60 had low $SpO_2$. Among these patients majority were in GOLD III and IV stages. The p value for this association is 0.000 (< 0.001). This is highly significant. Thus patients with lower $SpO_2$ had more severe COPD.

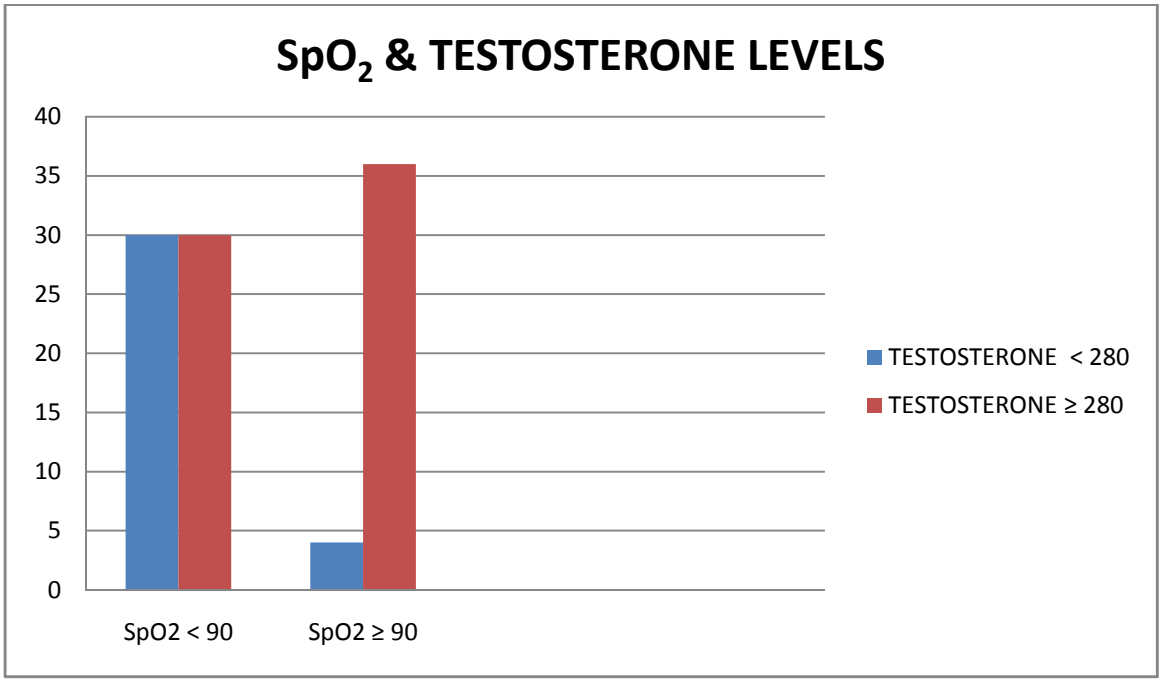

SpO2 & GOLD STAGE
30
25
20
15
10
5
0
SpO2 < 90
SpO2 ≥ 90
GOLD I
GOLD II
GOLD III
GOLD IV

**16) Comparison between $SpO_2$ and serum testosterone:**

| **$SpO_2$** | **PARAMETER** | **SERUM TESTOSTERONE** | |
|---|---|---|---|
| | | < 280 | ≥ 280 |
| < 90 | Count | 30 | 30 |
| | % within low $SpO_2$ group | 50 | 50 |
| ≥ 90 | Count | 4 | 36 |
| | % within low $SpO_2$ group | 10 | 90 |

Pearson Chi-Square test: p value: < 0.001 (highly significant)

Among the 60 patients with low $SpO_2$, 50% had low testosterone levels. The p value for this association is highly significant. Thus patients with lower $SpO_2$ had greater probability of having low testosterone levels compared to those with normal $SpO_2$.

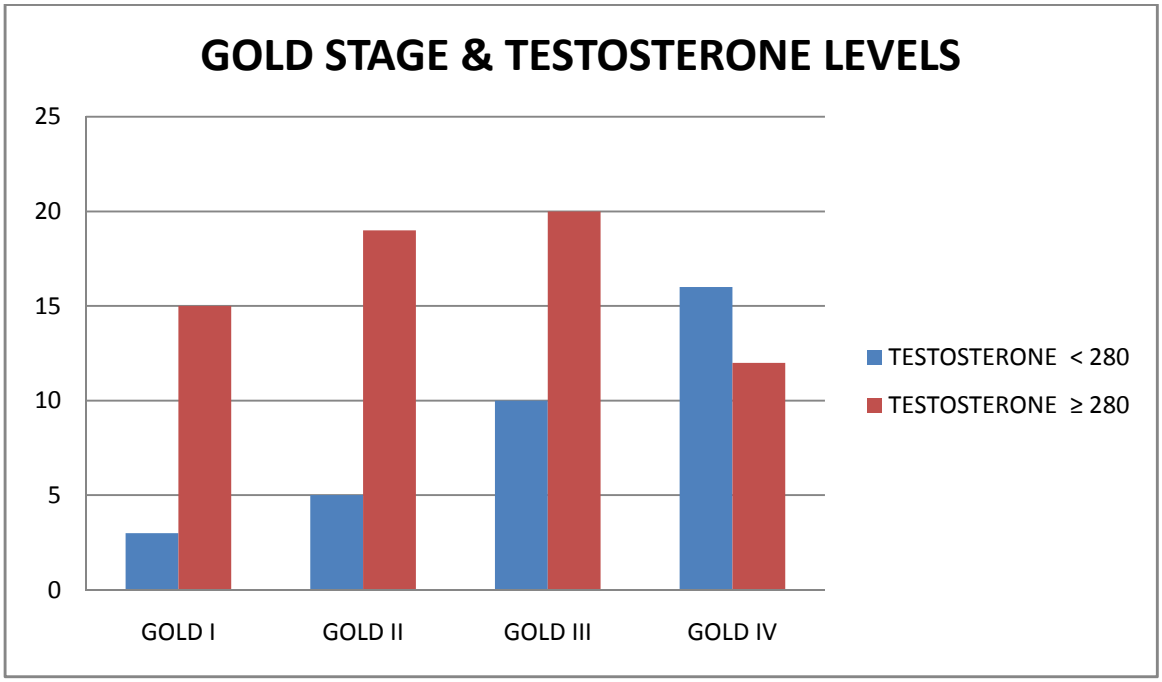

SpO2 & TESTOSTERONE LEVELS
40
35
30
25
20
15
10
5
0
SpO2 < 90
SpO2 ≥ 90
TESTOSTERONE < 280
TESTOSTERONE ≥ 280

**17) Comparison between serum testosterone and GOLD stage:**

| GOLD STAGE | PARAMETER | SERUM TESTOSTERONE | |
|---|---|---|---|
| | | < 280 | ≥ 280 |
| I | Count | 3 | 15 |
| | % within GOLD I | 16.7 | 83.3 |
| II | Count | 5 | 19 |
| | % within GOLD II | 20.8 | 79.2 |
| III | Count | 10 | 20 |
| | % within GOLD III | 33.3 | 66.7 |
| IV | Count | 16 | 12 |
| | % within GOLD IV | 57.1 | 42.9 |

Pearson Chi-Square test: p value – 0.012 (significant)

From the above table it is clearly demonstrated that as the COPD severity increased, the likelihood of having a low testosterone level increased. The p value for this association is 0.012 ($0.01 > p \leq 0.05$). This is a significant association.

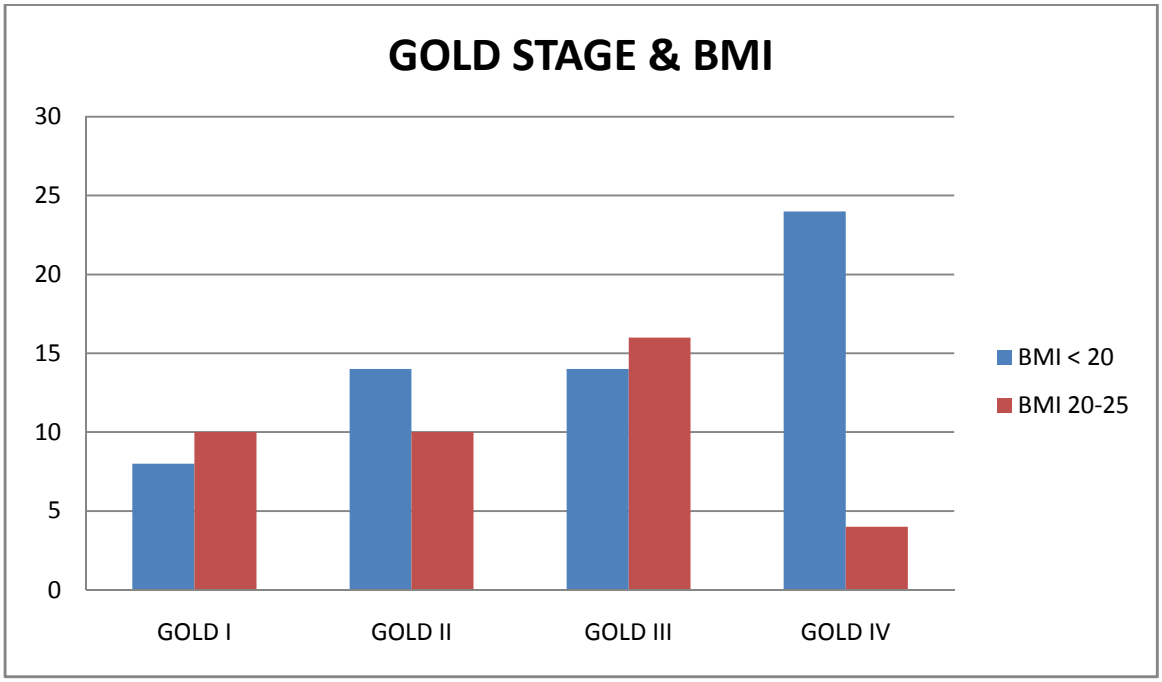

GOLD STAGE & TESTOSTERONE LEVELS
25
20
15
10
5
0
GOLD I
GOLD II
GOLD III
GOLD IV
TESTOSTERONE < 280
TESTOSTERONE ≥ 280

**18) Comparison between GOLD stage and BMI:**

| GOLD STAGE | PARAMETER | BMI ( $Kg/m^2$ ) | |
|---|---|---|---|
| | | < 20 | 20-25 |
| I | Count | 8 | 10 |
| | % within GOLD I | 44.4 | 55.6 |
| II | Count | 14 | 10 |
| | % within GOLD II | 58.3 | 41.7 |
| III | Count | 14 | 16 |
| | % within GOLD III | 46.7 | 53.3 |
| IV | Count | 24 | 4 |
| | % within GOLD IV | 85.7 | 14.3 |

Pearson Chi-Square test: p value: 0.008 (< 0.01, highly significant).

Although the percentage of patients with low body mass index in GOLD stages I to III are similar, the percentage of patients with low body mass index in GOLD IV is quite high (85.7%). Thus there is a tendency for low body mass index in very severe COPD patients in this study.

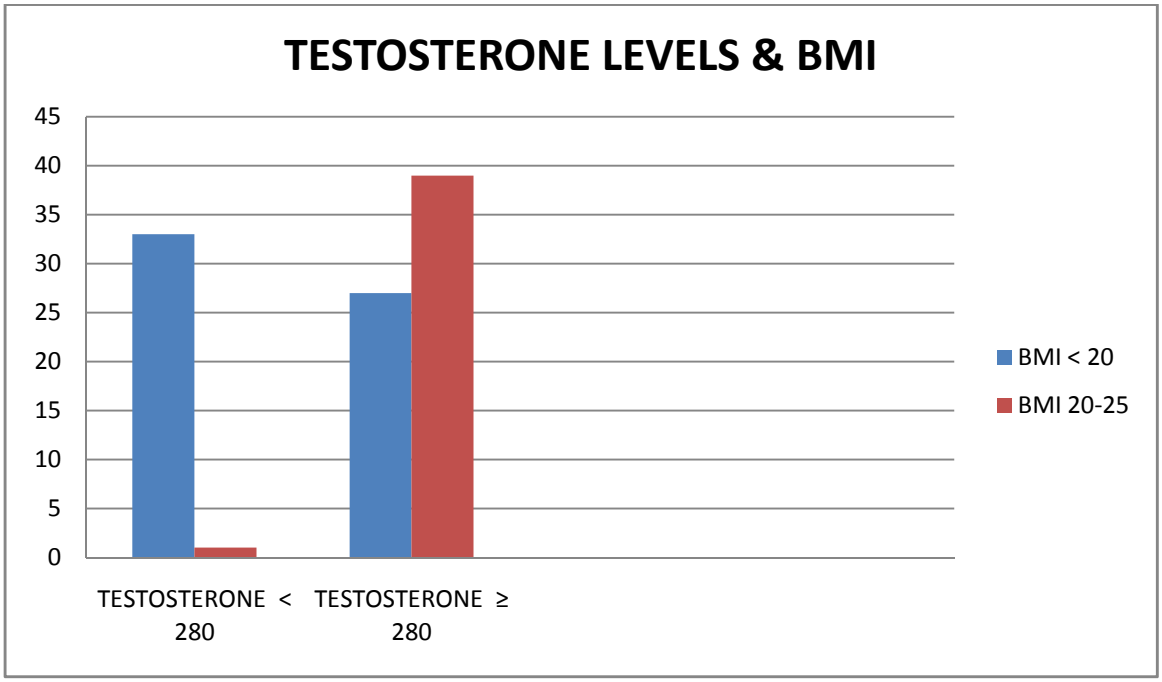

GOLD STAGE & BMI
30
25
20
15
10
5
0
GOLD I
GOLD II
GOLD III
GOLD IV
BMI < 20
BMI 20-25

**19) Comparison between serum testosterone and BMI:**

| **SERUM TESTOSTERONE** | **PARAMETER** | **BMI ( Kg/m$^2$ )** | |
|---|---|---|---|
| | | < 20 | 20-25 |
| < 280 ng/dl | Count | 33 | 1 |
| | % within low testosterone group | 97.1 | 2.9 |
| ≥ 280 ng/dl | Count | 27 | 39 |
| | % within normal testosterone group | 40.9 | 59.1 |

Pearson Chi-Square test: p value < 0.001 (highly significant).

Almost all patients with low testosterone levels had low BMI. This is a highly significant association as shown by the p value.

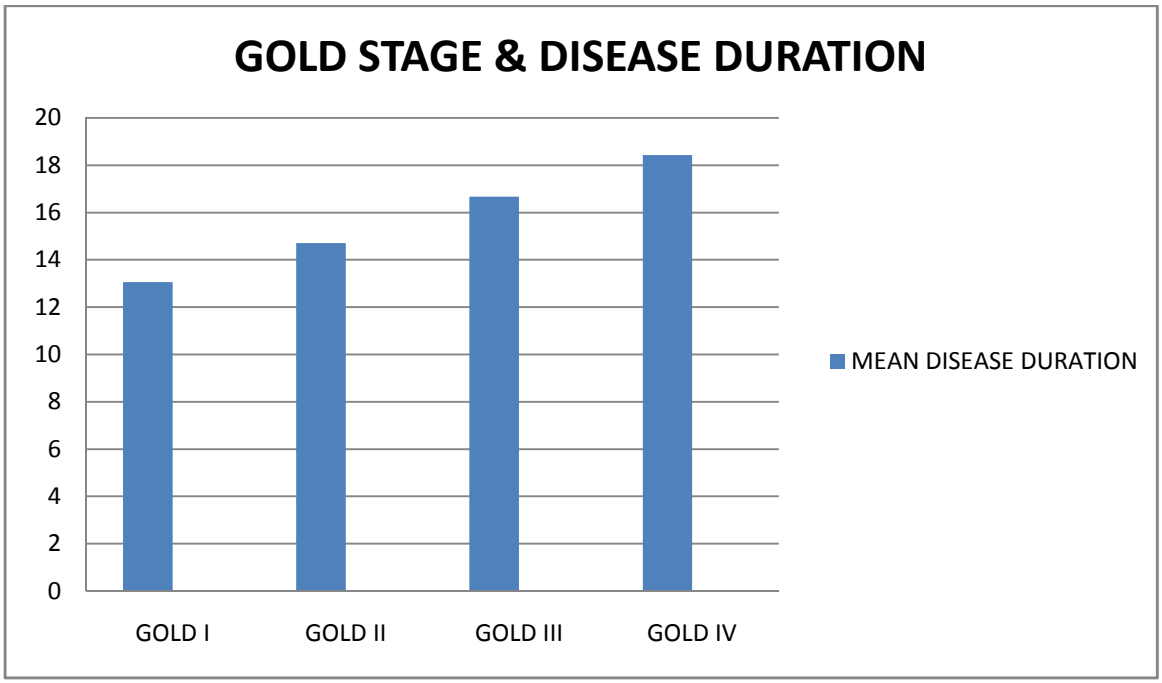

TESTOSTERONE LEVELS & BMI
45
40
35
30
25
20
15
10
5
0
TESTOSTERONE < 280
TESTOSTERONE ≥ 280
BMI < 20
BMI 20-25

**20) Comparison of disease duration and GOLD stage:**

| GOLD STAGE | NUMBER OF PATIENTS | MEAN DISEASE DURATION |
|---|---|---|
| I | 18 | 13.06 |
| II | 24 | 14.71 |
| III | 30 | 16.67 |
| IV | 28 | 18.43 |

ANOVA test: significance 0.000

The average disease duration increased from GOLD I to GOLD IV.

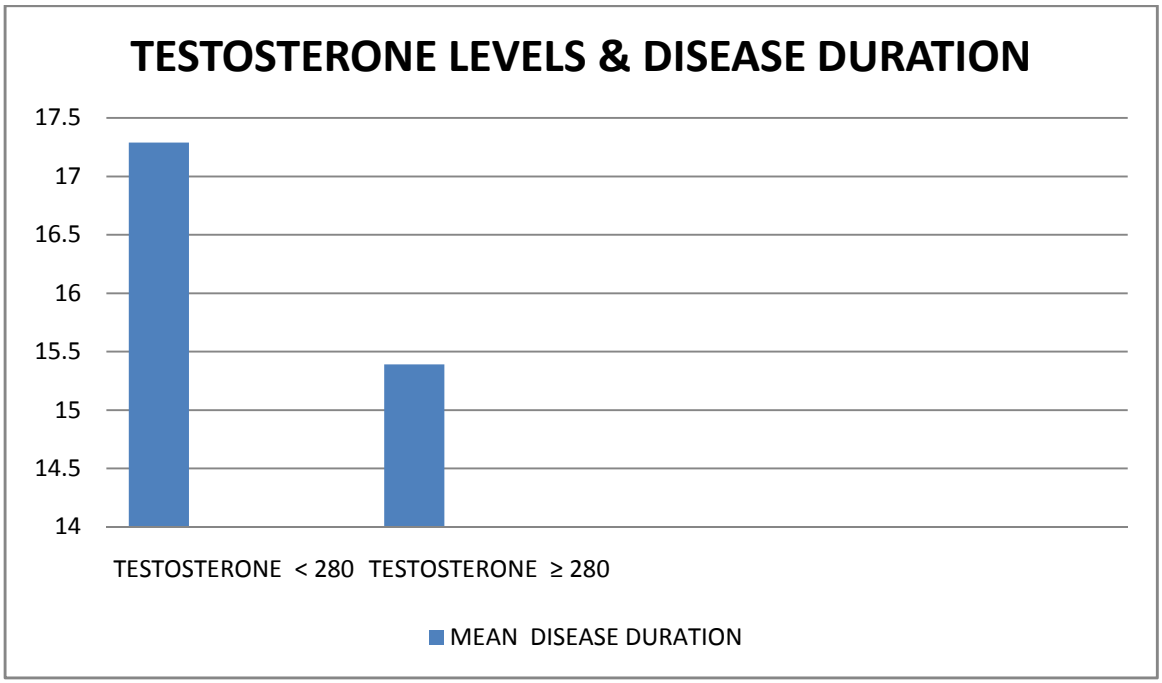

GOLD STAGE & DISEASE DURATION
20
18
16
14
12
10
8
6
4
2
0
GOLD I
GOLD II
GOLD III
GOLD IV
MEAN DISEASE DURATION

**21) Comparison of disease duration and serum testosterone levels:**

| **SERUM TESTOSTERONE ( ng/dl )** | **MEAN DISEASE DURATION** |
|---|---|
| < 280 | 17.29 |
| ≥ 280 | 15.39 |

T- test significance : 0.009

Average disease duration was higher in the low testosterone group.


TESTOSTERONE LEVELS & DISEASE DURATION
17.5
17
16.5
16
15.5
15
14.5
14
TESTOSTERONE < 280
TESTOSTERONE ≥ 280
MEAN DISEASE DURATION

# DISCUSSION

# DISCUSSION

Out of the 100 patients enrolled in the study, majority (66%) were in the age interval 51-60. Similarly maximum number of patients belonged to GOLD III & IV stages (58%).

Among the 100 patients, 34 had low testosterone levels. Various studies have yielded similar results (*Laghi et al 37%*). Low testosterone levels are more common in very severe COPD patients according to various studies[104-108]. The same trend is seen in this study (57.14% of patients with very severe COPD had low testosterone levels).

Of the 100 patients, 34 were on long term glucocorticoid treatment. Among these patients, 25 had low testosterone levels (73.5%) whereas only 13.6% among those not taking glucocorticoids had low testosterone levels.

Lower BMI was more common in the very severe COPD group. 40% of those with low BMI had very severe COPD.This finding was similar to the study done by Hsu et al.

More than half (55%) of the patients with low BMI had low testosterone levels. This is due to the fact that low testosterone levels could be one of the contributory factors for muscle wasting in COPD.

Half of the patients in this study with resting hypoxia had lower testosterone levels[108]. Hypoxia induced inhibition of gonadotropin secretion is a well known fact.

Correlation between low $FEV_1$ and low testosterone levels are known[104-108]. Similarly, in this study GOLD stage IV housed the maximum number of patients with low testosterone levels.

# CONCLUSION

# CONCLUSIONS

1) Patients in GOLD stage IV had higher probability of having low testosterone levels.
2) Patients had higher risk of low testosterone levels with decreasing oxygen saturation.
3) Patients showed a tendency of decreasing BMI with increasing disease severity.
4) Patients on long term glucocorticoid therapy had higher chances of having low testosterone levels.

# SUMMARY

# SUMMARY

The occurrence of low testosterone levels in COPD has been demonstrated by various studies[104-108]. However the percentage of patients having low testosterone levels varies widely among studies. In this study the prevalence of low testosterone levels was 34%.

The aetiology of low testosterone levels in COPD is multifactorial. They are direct effect of smoking on the testis, hypoxia induced inhibition of pituitary gonadotropin secretion, direct effect of hypoxia on Leydig cells and effect of long term glucocorticoid therapy.

The significance of low testosterone levels in COPD lies in the fact that it independently increases the mortality in this setting apart from affecting the quality of life[109]. Testosterone replacement therapy has been already tried in this setting with encouraging results. Further studies are needed in this area for better understanding and for improving therapeutic approaches.

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# BIBLIOGRAPHY


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# ANNEXURES

# ABBREVATIONS

| | | |
|---|---|---|
| ABG | - | Arterial Blood Gases |
| BMI | - | Body Mass Index |
| BOLD | - | Burden of Obstructive Lung Disease |
| cAMP | - | Cyclic Adenosine Mono Phosphate |
| CCF | - | Congestive Cardiac Failure |
| CD | - | Cluster Differentiation |
| CLIA | - | Chemi- Luminescence Immuno Assay |
| COPD | - | Chronic Obstructive Pulmonary Disease |
| CXR PA | - | Chest X-Ray Postero Anterior |
| DALY | - | Disability Adjusted Life Years |
| ELISA | - | Enzyme Linked Immuno- Sorbent Assay |
| $FEV_1$ | - | Forced Expiratory Volume in 1 second |
| FRC | - | Functional Residual Capacity |
| FSH | - | Follicle Stimulating Hormone |
| FVC | - | Forced Vital Capacity |
| GOLD | - | Global initiative for chronic Obstructive Lung Disease |
| GORD | - | Gastro Oesophageal Reflux Disease |
| GnRH | - | Gonadotropin Releasing Hormone |
| HDL | - | High Density Lipoprotein |

| | | |
|---|---|---|
| HIV | - | Human Immunodeficiency Virus |
| HRCT | - | High Resolution Computerised Tomography |
| HU | - | Hounsfield Unit |
| ICU | - | Intensive Care Unit |
| IL-6,8& 1β | - | Interleukin-6,8 & 1β |
| INSEARCH- | | Indian Study on Epidemiology of Asthma, Respiratory symptoms and Chronic Bronchitis |
| LH | - | Luteinizing Hormone |
| LMW heparin | - | Low Molecular Weight heparin |
| $LTB_4$ | - | Leukotiene $B_4$ |
| LVRS | - | Lung Volume Reduction Surgery |
| MRC | - | Medical Research Council |
| NICE | - | National Institute for Health and Clinical Excellence |
| NIPPV | - | Non Invasive Positive Pressure Ventilation |
| PAH | - | Pulmonary Artery Hypertension |
| PDE-4 | - | Phosphodiesterase-4 |
| REM | - | Rapid Eye Movement |
| RV | - | Residual Volume |
| SHBG | - | Sex Hormone Binding Globulin |
| SPSS | - | Statistical Package for the Social Sciences |

| | | |
|---|---|---|
| StAR | - | Steroidogenic Acute Regulatory protein |
| TGF β | - | Transforming Growth Factor β |
| TIMP | - | Tissue Inhibitor of Matrix metalloproteinase |
| TLC | - | Total Lung Capacity |
| TNF | - | Tumour Necrosis Factor |
| TSH | - | Thyroid Stimulating Hormone |
| UK | - | United kingdom |
| USA | - | United States of America |
| VC | - | Vital Capacity |
| V/Q | - | Ventilation- Perfusion |
| YLD | - | Years of Living with Disability |

**SERUM TESTOSTERONE LEVELS IN MALE**

**COPD PATIENTS**

Name : Patient ID No:

Age : Contact No:

Occupation :

Complaints:

Symptomatics of COPD with

-erectile dysfunction

- poor morning erection

- loss of ejaculation

- low libido

Past history:

DM, SHT, TB, CAD, CKD, Malignancy, Surgery

Personal history:

- Smoking

- Alcohol

- Drugs

General Examination:

Pulse-

BP-

Height-

Weight-

BMI-

SPO2-

Systemic Examination:

CVS-

RS-

P/A-

CNS-

Investigations:

CXR PA view-

Pulmonary function test-

Serum testosterone-

FBS-

PPBS-

HIV Elisa-

Renal function test-

Liver Function test-

USG Abdomen-

ECG-

Echocardiogram-

Thyroid profile-

# INSTITUTIONAL ETHICS COMMITTEE
# MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No : 044 25305301
Fax : 044 25363970

## CERTIFICATE OF APPROVAL

To
Dr. D. Henith Raj,
Post Graduate, MD (General Medicine)
Institute of Internal Medicine,
Madras Medical College,
Chennai – 600003.

Dear Dr. D. Henith Raj,

The Institutional Ethics Committee has considered your request and approved your study titled **"SERUM TESTOSTERONE LEVELS IN MALE COPD PATIENTS"** No. 36072014.

The following members of Ethics Committee were present in the meeting held on 01.07.2014 conducted at Madras Medical College, Chennai-3.

| | | |
|---|---|---|
| 1. | Dr. C. Rajendran, M.D. | -- Chairperson |
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| 11. | Thiru. S. Govindasamy, BABL, High Court, Chennai-1. | -- Lawyer |
| 12. | Tmt. Arnold Saulina, MA MSW | -- Social Scientist |

We approve the proposal to be conducted in its presented form.

Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

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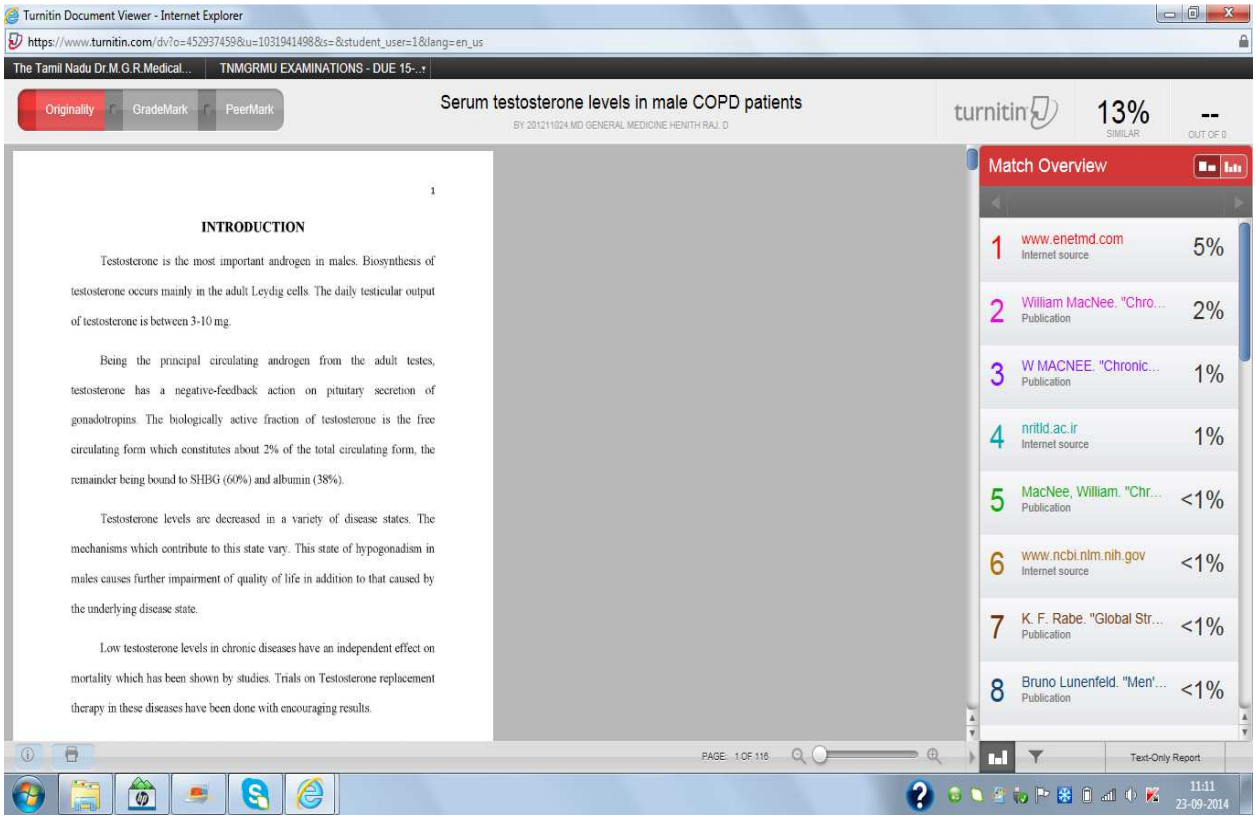

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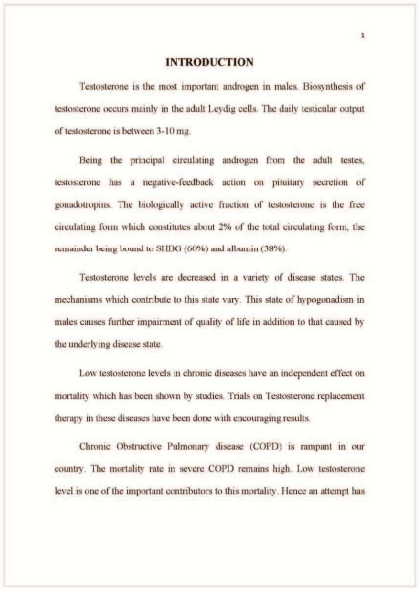

1

**INTRODUCTION**

Testosterone is the most important androgen in males. Biosynthesis of testosterone occurs mainly in the adult Leydig cells. The daily testicular output of testosterone is between 3-10 mg.

Being the principal circulating androgen from the adult testes, testosterone has a negative-feedback action on pituitary secretion of gonadotropins. The biologically active fraction of testosterone is the free circulating form which constitutes about 2% of the total circulating form, the remainder being bound to SHBG (60%) and albumin (38%).

Testosterone levels are decreased in a variety of disease states. The mechanisms which contribute to this state vary. This state of hypogonadism in males causes further impairment of quality of life in addition to that caused by the underlying disease state.

Low testosterone levels in chronic diseases have an independent effect on mortality which has been shown by studies. Trials on Testosterone replacement therapy in these diseases have been done with encouraging results.

Chronic Obstructive Pulmonary disease (COPD) is rampant in our country. The mortality rate in severe COPD remains high. Low testosterone level is one of the important contributors to this mortality. Hence an attempt has

| S.No | IP No. | AGE ( years) | SMOKING | GLUCOCORTCOID TREATMENT | DISEASE DURATION ( years ) | BMI (Kg/m2) | SPO2( mmHg) | FEV1( % 0f pred.) | FEV1/FVC | GOLD STAGE | SERUM TESTOSTERONE ( ng/dl ) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 127558 | 58 | + | - | 15 | 19.46 | 89 | 81 | 69 | I | 301.5 |
| 2 | 127559 | 51 | + | + | 15 | 19.01 | 86 | 40 | 42 | III | 261.7 |
| 3 | 127567 | 60 | + | - | 16 | 19.94 | 90 | 51 | 52 | II | 312 |
| 4 | 127579 | 52 | + | - | 15 | 15.61 | 83 | 28 | 39 | IV | 192.3 |
| 5 | 127590 | 54 | + | - | 20 | 15.05 | 83 | 26 | 37 | IV | 191.2 |
| 6 | 127601 | 49 | + | + | 12 | 20.05 | 90 | 41 | 40 | III | 319.1 |
| 7 | 127633 | 60 | + | - | 15 | 17.91 | 86 | 29 | 36 | IV | 311.8 |
| 8 | 127639 | 56 | + | - | 10 | 20.23 | 89 | 38 | 35 | III | 332 |
| 9 | 127678 | 48 | + | - | 12 | 19.88 | 88 | 40 | 39 | III | 396.9 |
| 10 | 127699 | 61 | + | - | 20 | 18.81 | 87 | 34 | 41 | III | 249.5 |
| 11 | 128001 | 58 | + | + | 17 | 15.77 | 83 | 26 | 31 | IV | 200.6 |
| 12 | 128019 | 51 | + | - | 20 | 16.73 | 83 | 26 | 38 | IV | 231.7 |
| 13 | 128039 | 62 | + | + | 20 | 15.83 | 82 | 28 | 35 | IV | 201.3 |
| 14 | 128045 | 52 | + | - | 15 | 19.44 | 91 | 66 | 65 | II | 432.2 |
| 15 | 128079 | 48 | + | - | 12 | 20.59 | 93 | 80 | 68 | I | 496.9 |
| 16 | 128093 | 60 | + | - | 15 | 19.48 | 90 | 81 | 67 | I | 270 |
| 17 | 128111 | 66 | + | - | 20 | 20.36 | 92 | 42 | 49 | III | 367.2 |
| 18 | 128134 | 59 | + | + | 25 | 20.17 | 85 | 25 | 35 | IV | 339.2 |
| 19 | 128756 | 60 | + | + | 20 | 15.52 | 82 | 25 | 39 | IV | 167.8 |
| 20 | 128789 | 50 | + | + | 15 | 18.22 | 85 | 32 | 41 | III | 256.6 |

| S.No | IP No. | AGE ( years) | SMOKING | GLUCOCORTICOID TREATMENT | DISEASE DURATION ( years ) | BMI (Kg/m2) | SPO2( mmHg) | FEV1( % 0f pred.) | FEV1/FVC | GOLD STAGE | SERUM TESTOSTERONE ( ng/dl ) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 21 | 128798 | 49 | + | + | 15 | 20.13 | 87 | 49 | 45 | III | 266.1 |
| 22 | 128804 | 50 | + | - | 15 | 19.23 | 86 | 27 | 40 | IV | 331.8 |
| 23 | 128809 | 55 | + | - | 20 | 18.88 | 86 | 26 | 38 | IV | 357.5 |
| 24 | 128843 | 59 | + | - | 20 | 20.28 | 86 | 45 | 46 | III | 309.9 |
| 25 | 128867 | 54 | + | - | 15 | 19.84 | 90 | 66 | 69 | II | 339.8 |
| 26 | 129345 | 50 | + | - | 12 | 20.66 | 94 | 70 | 65 | II | 416.2 |
| 27 | 129349 | 46 | + | - | 10 | 22.94 | 92 | 81 | 67 | I | 417.7 |
| 28 | 129357 | 49 | + | - | 12 | 21.59 | 94 | 81 | 68 | I | 467.3 |
| 29 | 129377 | 48 | + | - | 12 | 19.59 | 91 | 75 | 66 | II | 451.9 |
| 30 | 129399 | 56 | + | + | 20 | 18.72 | 88 | 47 | 51 | III | 265.9 |
| 31 | 129413 | 55 | + | - | 18 | 20.15 | 91 | 57 | 54 | II | 342.1 |
| 32 | 129444 | 52 | + | - | 15 | 20.64 | 90 | 42 | 50 | III | 387.3 |
| 33 | 129941 | 69 | + | - | 20 | 19.61 | 89 | 45 | 51 | III | 344.8 |
| 34 | 129990 | 53 | + | + | 15 | 18.89 | 86 | 36 | 42 | III | 236.8 |
| 35 | 129996 | 56 | + | - | 15 | 20.45 | 90 | 60 | 61 | II | 319.9 |
| 36 | 130497 | 52 | + | - | 15 | 19.89 | 92 | 66 | 64 | II | 352.4 |
| 37 | 130546 | 67 | + | - | 20 | 20.17 | 88 | 28 | 34 | IV | 338.6 |
| 38 | 130550 | 60 | + | - | 15 | 18.56 | 90 | 82 | 68 | I | 314.6 |
| 39 | 130552 | 59 | + | + | 18 | 16.9 | 85 | 26 | 32 | IV | 210.8 |
| 40 | 130559 | 66 | + | - | 25 | 19.02 | 89 | 29 | 36 | IV | 321.5 |

| S.No. | IP No. | AGE ( years) | SMOKING | GLUCOCORTICOID TREATMENT | DISEASE DURATION ( years ) | BMI (Kg/m2) | SPO2( mmHg) | FEV1( % 0f pred.) | FEV1/FVC | GOLD STAGE | SERUM TESTOSTERONE ( ng/dl ) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 41 | 130567 | 51 | + | + | 15 | 20.87 | 91 | 44 | 48 | III | 391.1 |
| 42 | 130595 | 53 | + | + | 18 | 20.46 | 89 | 46 | 49 | III | 421.4 |
| 43 | 130607 | 60 | + | - | 20 | 19.1 | 89 | 59 | 61 | II | 359.5 |
| 44 | 130614 | 60 | + | + | 20 | 19.17 | 87 | 46 | 51 | III | 251 |
| 45 | 130619 | 46 | + | - | 12 | 20.29 | 90 | 66 | 61 | II | 399.6 |
| 46 | 130645 | 50 | + | - | 15 | 19.55 | 91 | 71 | 65 | 11 | 372.7 |
| 47 | 130646 | 53 | + | - | 12 | 20.93 | 92 | 82 | 69 | I | 411.1 |
| 48 | 131123 | 56 | + | + | 20 | 17.33 | 82 | 29 | 36 | IV | 197.6 |
| 49 | 131145 | 53 | + | + | 17 | 16.04 | 83 | 26 | 37 | IV | 211.8 |
| 50 | 131154 | 59 | + | - | 20 | 21.18 | 91 | 46 | 50 | III | 405.5 |
| 51 | 131167 | 67 | + | - | 22 | 20.07 | 87 | 47 | 52 | III | 327 |
| 52 | 131170 | 52 | + | + | 15 | 19.05 | 86 | 45 | 50 | III | 250.9 |
| 53 | 131186 | 71 | + | - | 20 | 18.91 | 90 | 81 | 66 | I | 308.7 |
| 54 | 131196 | 52 | + | - | 15 | 19.64 | 85 | 26 | 38 | IV | 320.2 |
| 55 | 131200 | 60 | + | + | 20 | 19.45 | 89 | 69 | 67 | II | 265.9 |
| 56 | 131222 | 48 | + | - | 10 | 20.77 | 91 | 81 | 67 | I | 429.6 |
| 57 | 131229 | 51 | + | - | 15 | 19.78 | 89 | 81 | 67 | I | 333.8 |
| 58 | 131242 | 56 | + | - | 16 | 21.06 | 90 | 45 | 50 | III | 361.2 |
| 59 | 131255 | 59 | + | - | 15 | 20.79 | 87 | 47 | 54 | III | 324.8 |
| 60 | 131269 | 62 | + | + | 20 | 19.96 | 89 | 61 | 62 | II | 258 |

| S.No | IP No | AGE ( years) | SMOKING | GLUCOCORTICOID TREATMENT | DISEASE DURATION ( years ) | BMI (Kg/m2) | SPO2( mmHg) | FEV1( % 0f pred.) | FEV1/FVC | GOLD STAGE | SERUM TESTOSTERONE ( ng/dl ) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 61 | 131879 | 50 | + | - | 10 | 22.66 | 93 | 81 | 68 | I | 466.4 |
| 62 | 131888 | 59 | + | - | 15 | 20.15 | 89 | 43 | 49 | III | 306.9 |
| 63 | 131902 | 54 | + | - | 12 | 20.33 | 92 | 70 | 64 | II | 404.8 |
| 64 | 131909 | 61 | + | - | 15 | 20.15 | 89 | 58 | 64 | II | 393.1 |
| 65 | 131923 | 55 | + | + | 20 | 16.55 | 83 | 25 | 40 | IV | 206.6 |
| 66 | 131930 | 58 | + | + | 15 | 16.57 | 84 | 28 | 44 | IV | 222.5 |
| 67 | 131936 | 57 | + | + | 17 | 20.09 | 88 | 29 | 39 | IV | 321.8 |
| 68 | 131945 | 50 | + | - | 10 | 20.59 | 91 | 82 | 68 | I | 444.8 |
| 69 | 131957 | 56 | + | + | 15 | 19.77 | 90 | 65 | 60 | II | 266.2 |
| 70 | 131966 | 60 | + | + | 20 | 19.56 | 88 | 28 | 40 | IV | 307.1 |
| 71 | 132504 | 63 | + | - | 20 | 19.79 | 90 | 41 | 47 | III | 315.3 |
| 72 | 132525 | 52 | + | - | 12 | 23.17 | 94 | 81 | 68 | I | 442.9 |
| 73 | 132533 | 55 | + | - | 12 | 19.65 | 92 | 81 | 67 | I | 260.9 |
| 74 | 132543 | 59 | + | - | 15 | 20.55 | 89 | 49 | 51 | III | 327.2 |
| 75 | 132548 | 54 | + | - | 12 | 19.05 | 89 | 71 | 64 | II | 269.7 |
| 76 | 132564 | 58 | + | + | 18 | 16.55 | 82 | 27 | 43 | IV | 214.6 |
| 77 | 132999 | 58 | + | + | 15 | 16.45 | 82 | 27 | 38 | IV | 205.3 |
| 78 | 133007 | 62 | + | - | 18 | 18.21 | 88 | 41 | 48 | III | 328.9 |
| 79 | 133009 | 60 | + | + | 20 | 15.42 | 83 | 25 | 37 | IV | 181 |
| 80 | 133020 | 55 | + | - | 15 | 19.65 | 86 | 42 | 51 | III | 264.7 |

| S.No | IP No | AGE ( years) | SMOKING | GLUCOCORTICOID TREATMENT | DISEASE DURATION ( years ) | BMI (Kg/m2) | SPO2( mmHg) | FEV1( % 0f pred.) | FEV1/FVC | GOLD STAGE | SERUM TESTOSTERONE ( ng/dl ) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 81 | 133026 | 47 | + | + | 10 | 20.23 | 92 | 71 | 66 | II | 448.6 |
| 82 | 133042 | 55 | + | + | 15 | 19.16 | 89 | 61 | 65 | II | 269.3 |
| 83 | 133058 | 60 | + | - | 18 | 19.16 | 90 | 82 | 67 | I | 207.1 |
| 84 | 133070 | 61 | + | + | 20 | 15.08 | 83 | 25 | 36 | IV | 151.7 |
| 85 | 133678 | 56 | + | - | 16 | 18.72 | 86 | 46 | 53 | III | 334.5 |
| 86 | 133687 | 53 | + | + | 18 | 18.42 | 86 | 37 | 43 | III | 244.4 |
| 87 | 133695 | 53 | + | - | 15 | 19.33 | 90 | 59 | 58 | II | 356.2 |
| 88 | 133699 | 54 | + | - | 15 | 18.91 | 91 | 64 | 62 | II | 354.6 |
| 89 | 133708 | 45 | + | - | 7 | 20.12 | 93 | 81 | 68 | I | 377.5 |
| 90 | 133724 | 56 | + | + | 18 | 16.08 | 83 | 29 | 38 | IV | 189.8 |
| 91 | 134145 | 58 | + | + | 18 | 19.23 | 87 | 29 | 39 | IV | 301.8 |
| 92 | 134155 | 54 | + | - | 15 | 22.89 | 93 | 82 | 68 | I | 492.8 |
| 93 | 134167 | 55 | + | - | 15 | 20.13 | 86 | 29 | 41 | IV | 335.5 |
| 94 | 134169 | 60 | + | - | 18 | 19.71 | 86 | 28 | 37 | IV | 350 |
| 95 | 134178 | 59 | + | + | 18 | 21.48 | 89 | 67 | 62 | II | 349.8 |
| 96 | 134198 | 46 | + | - | 12 | 21.62 | 92 | 69 | 66 | II | 345.7 |
| 97 | 134223 | 49 | + | - | 12 | 19.58 | 90 | 65 | 67 | II | 392.2 |
| 98 | 134227 | 57 | + | - | 15 | 20.68 | 89 | 48 | 52 | III | 328.1 |
| 99 | 134245 | 61 | + | - | 18 | 20.18 | 87 | 43 | 47 | III | 321.7 |
| 100 | 134257 | 48 | + | - | 12 | 21.08 | 92 | 75 | 67 | II | 446.3 |